

INTERMEDIATES IN AROMATIC

SUBSTITUTION REACTIONS

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by

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Abstract

A systematic study has been made of the protonation of methyl- and ethylphenols and methylnaphthols in fluorosulphuric acid.

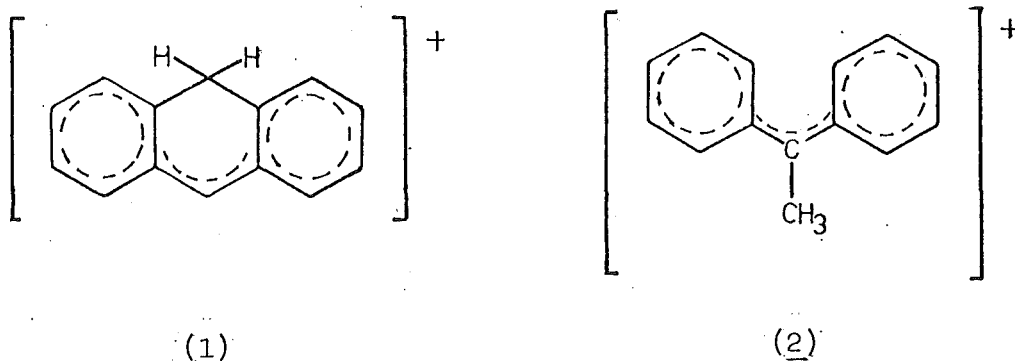
As well as the expected steric and electronic directional influences of the substituents, solvent effects are also found to have an important bearing on the site of electrophilic attack. Protonation may take place either on the oxygen substituent or on the aromatic ring; comparison with other studies shows the former to be favoured in good hydrogen-bonding solvents.

The preferred site for ring-attack is para to the hydroxyl group, but alkyl substitution of this site deactivates it towards proton attack by restricting solvation of the cation formed. The major site of attack will then be either ortho to the hydroxyl group or on oxygen unless protonation of a substituted site is favoured by the release of steric strain.

The alkyl groups are much more weakly ortho-para directing than the oxygen substituent, so their electronic influences are not as important as their steric clashes, both with solvating species and with neighbouring substituents, which can be major factors controlling the site of protonation.

INTRODUCTION

It is now well established that the cationic species formed from aromatic precursors in solvents of high acidity are carbocations,, i.e. the acid proton adds to the arene by forming a new carbon-hydrogen σ -bond. The first clear indication of this was reported in 1952 by Gold and Tye¹, who concluded that the close similarity of the absorption spectra of the "proton complexes" of anthracene (1) and 1,1-diphenylethylene (2) can only be



interpreted in terms of identical π -electron structures, which result when the added protons are σ -bonded in the respective proton adducts. Further evidence was put forward by Dallinga, Mackor, and Verrijn Stuart², who observed the spectra of a series of protonated arenes and obtained good agreement with those calculated quantum mechanically for the postulated carbocations. However the most conclusive evidence came in 1958 when MacLean, van der Waals and Mackor³ were able to show the presence of paraffinic CH_2 and CHCH_3 groups in the conjugate acids of some arenes from the chemical shifts and hyperfine splittings of the NMR signals of these groups.

Arenonium ions and their derivatives occur as intermediates

in a great variety of electrophilic substitution reactions, and many other acid-catalysed reactions in which aromatic compounds take part. The hypothesis advanced for the first time by Pfeiffer and Wizinger⁴ in 1928, and later generalized by Wheland⁵, that electrophilic substitution reactions proceed via a carbocation intermediate has been generally accepted, and consequently any information on the physical and chemical properties of arenonium ions may have a direct bearing on our understanding of these reactions.

Early experimental studies of arenonium ions mainly concerned the basicity of arenes and electronic spectra of the cations. However, as NMR techniques became available, research in the field entered a new stage. Nuclear magnetic resonance has been used extensively in the elucidation of structure, and as well as structural information, indications of the charge density at various sites in the ion have been obtained. In addition, NMR can be used, in a number of cases, to determine rates of inter- and intramolecular processes, including rates of conformational changes in protonated molecules.

However, it is important to appreciate the limiting factor associated with the exchange of acidic protons in the protonated molecule with the solvent. For observation of separate resonances in the NMR spectrum, the lifetime of the acidic proton on the site of protonation must be at least 10^{-1} - 10^{-2} seconds. The lifetime of the proton in a solvent of given acidity will be dependent on the basicity of the site protonated and also on the temperature. For a given site, the rate of exchange of the acidic proton will, in general, decrease with increasing acidity of the medium. Thus the most favourable

conditions for observing an acidic proton by NMR will be at low temperature and in a medium of high acidity. It is for this reason that "superacid" systems and the use of low-temperature NMR spectroscopy has led to the direct observation of a considerable number of protonated weak bases, under conditions where the exchange rate with the solvent is low enough to observe the acidic proton directly.

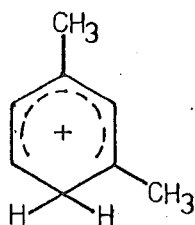
Fluorosulphuric acid (FSO_3H) is one of the strongest of the simple protic acids. Only disulphuric acid ($\text{H}_2\text{S}_2\text{O}_7$) appears to be more acidic than 100% fluorosulphuric acid. Moreover the acidity of fluorosulphuric acid (and of HF) can be considerably increased by the addition of SbF_5 and $\text{SbF}_5\text{-SO}_3$. For example, FSO_3H has an H_0 value of -12.8, whereas 1:1 $\text{FSO}_3\text{H}:\text{SbF}_5$ has an H_0 of -17.5 to -18. These solutions are amongst the most highly acidic media known, and are justifiably called superacid media.

Spectra of arenonium ions have been measured in $\text{HF}+\text{BF}_3$ ^{6,7}; $\text{HF}+\text{SbF}_5$ ⁶, FSO_3H ^{8,9} or $\text{FSO}_3\text{H}+\text{SbF}_5$ ^{10,11}, $\text{CF}_3\text{COOH}+\text{H}_2\text{O}\cdot\text{BF}_3$ ¹², and for rather more basic substrates in H_2SO_4 and HClO_4 ^{13,14}. The use of low temperatures, both to decrease the rate of exchange and also to prevent further reaction of the ion can lead to experimental difficulties due to the viscosity of the acid system causing peak broadening in the NMR spectrum. This problem has been overcome by employing such diluents as SO_2 and SO_2ClF , which do not appreciably diminish the acidity of the system¹⁵.

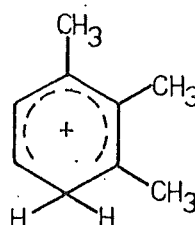
The conjugate acid of an arene will always comprise an equilibrium mixture of ions formed by the protonation of the parent

base at different sites, but usually only one, or in some cases two, of the isomeric ions will predominate strongly over all the others. The equilibria between protonated species are dependent upon the relative energies of the ions. At -50° a free energy difference of 1.5 kJ mol^{-1} between two isomeric ions will result in the formation of the more stable ion being favoured to the extent of 97%, and the minor ion may not be detected experimentally.

This absence of isomeric products is a feature of the cations derived from the polymethylbenzenes, which were amongst the first species to be studied under suitable conditions of temperature and acid strength^{3,6,7,8,16}. It was quickly found that only one ion was obtained from each precursor, the favoured sites being those ortho and para to the alkyl groups as is seen in the ions derived from m-xylene (3) and hemimellitene (4) shown below:



(3)

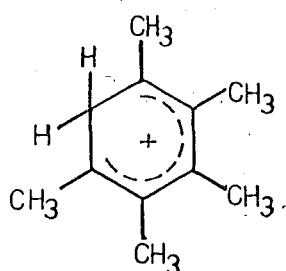


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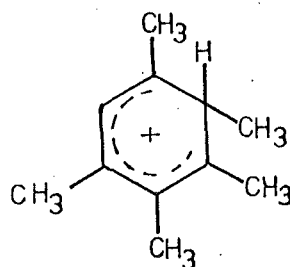
Basicity measurements indicate that, other things being equal, the basicity of a site is enhanced somewhat more by a methyl group in the para position than in the ortho position, and deuteration and de-deuteration experiments with toluene^{17,18} lead to the estimation that the basicity-increasing effect of a para methyl group is about twice that of an ortho methyl group. However the results of NMR spectroscopic work indicate a higher value, and, possibly because of the energy considerations mentioned above, it appears that the

preference for a para site, which is only slight at room temperature is more appreciable at the lower temperatures at which the cations are generated.

The introduction of a methyl group at the reactive site decreases its basicity. This is strikingly illustrated by the pentamethylbenzenonium ion (5), where one might have expected



(5a)



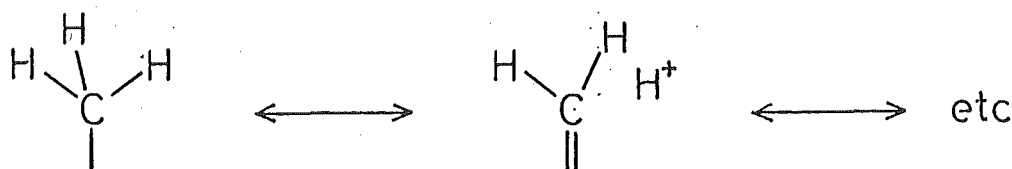
(5b)

the $2H^+$ isomer (5b) to be present in addition to the $6H^+$ isomer (5a), as the former, in comparison with the latter, lacks only the weak stabilization of a meta methyl group and is favoured by a statistical advantage of two. The $2H^+$ isomer should be readily detectable by the characteristic $CHCH_3$ signals in the NMR spectrum, but there is no evidence for its existence. Confirmatory evidence that an ipso* methyl group lowers the basicity at the reactive site comes from the lack of para protonation in p-methylanisole compared with anisole, and the observation that methyl substitution at the 3-position in indole and methylindoles decreases the basicity of that site by a factor of $10-20^{20}$.

It has been postulated that this effect could be explained qualitatively by considering that the hyperconjugative interaction

* "ipso" position - the position bearing the substituent¹⁹.

energy of the methyl group in the molecule is lost on its reverting to an aliphatically bonded group in the cation²¹. Some evidence to support this came from molecular orbital calculations²². Charge density distributions were calculated using the CNDO method for methylbenzenes and the most stable of the benzenonium ions derived from each. These figures show that methyl-bearing carbons in the aromatic hydrocarbons tend to be slightly electron deficient; hydrogen-bearing carbon atoms ortho and para to them, and methyl groups, are of rather high electron density, and those meta slightly low. A very different pattern of electron distribution emerges upon protonation of an aromatic molecule. Much larger disparities of charge are found, a considerable amount of charge being transferred from a methyl group to the conjugated part of the ring. As found for simple cations²³, the positive charge is resident mainly on hydrogen. These figures are in accordance with the valence bond formulation of hyperconjugation (6) by the methyl group.

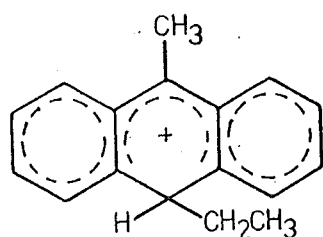
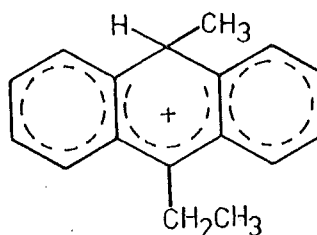


(6)

The centres of electron deficiency in the benzenonium ions are calculated to be at positions 2, 4, and 6 as experimentally observed by ¹³CMR²⁴.

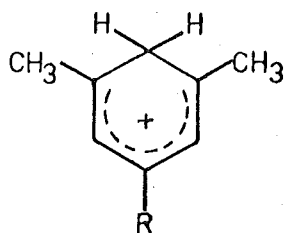
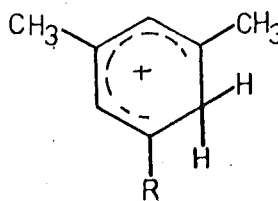
The search for experimental evidence for hyperconjugative interactions in arenonium ions has caused a certain amount of debate in the literature. Arnett and Larsen²⁵ measured the heats

of formation of benzenonium ions derived from various alkylbenzenes in $\text{SbF}_5\text{-FSO}_3\text{H}$ solutions. They discovered a very large Baker-Nathan effect which they explained in terms of hyperconjugation and steric inhibition of solvation. However, shortly afterwards Brouwer and van Doorn¹² tested this theory by protonating 9-methyl-10-ethylanthracene in HF to get a mixture of two isomers, (7a) and (7b):

(7a)(7b)

They found a product ratio which varied with temperature, with (7a) being favoured over (7b) by a factor of 7.5:1 at -20° and 4.0:1 at $+70^\circ$. As protonation ipso to the ethyl group releases some of the steric strain with the α -hydrogens, it would appear that the ethyl and methyl groups are approximately equal in ability to stabilize the carbonium ion, and that hyperconjugation is not a factor here.

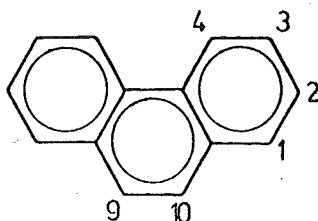
A similar type of investigation was carried out by Koptug et al²⁶, who protonated a series of 5-substituted m-xylenes and obtained two products, (8a) and (8b):

(8a)(8b)

For the series $R = C_2H_5$, iso- C_3H_7 , tert- C_4H_9 , the statistical ratio (8b): (8a) should be 2:1. While this (8b): (8a) ratio was obtained for $R = C_2H_5$, the ratio for $R =$ tert.-butyl was nearly 5:1. The Russians took these results as supporting the hyperconjugative mechanism of stabilization, while pointing out that the effect is considerably smaller than that seen in Arnett and Larsen's work.

However despite this evidence the hyperconjugation theory must be regarded as doubtful following the recent publication²⁷ of results which show that while in the gas phase alkyl groups follow the inductive order in their ability to stabilize protonated benzene, they follow the Baker-Nathan order in superacid solution. This implies that the larger alkyl groups are sterically hindering solvent stabilization of the cation, and thus that the deactivation of a basic site by an ipso methyl group may be just another manifestation of the solvent effects which will later be seen to be so important to the stability of benzenonium ions in solution.

Provided the solvent used is sufficiently acidic to protonate the ring, there is no variation with the acid system of the position of protonation in the methylbenzenes. The variation in size of the protonating species in the different acid media appears to have no effect except in sterically very crowded situations. The protonation of biphenyl²⁸, for example, occurs at the ortho position in $HF-BF_3$, but in SbF_5-OSO_3H para-protonation is observed. This difference is attributed to the bulk of the attacking agent in the transition state of the proton transfer process. A similar situation is observed in phenanthrene (9) where in $HF-BF_3$ at -70° a mixture of 9- and 4-

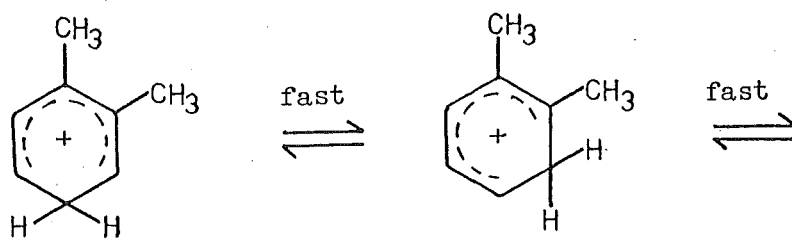


(9)

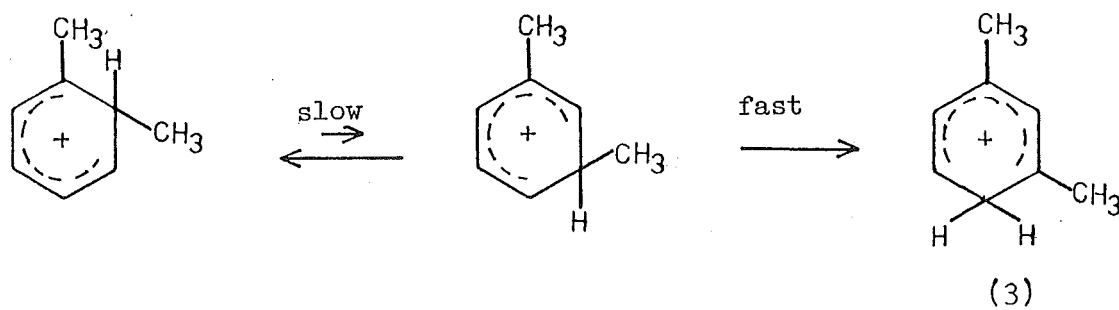
phenanthrenium ions is obtained, but in $\text{SbF}_5\text{-FSO}_3\text{H}$ there is only a very small amount of attack at the 4- position²⁸.

The stability of an arenonium ion is determined by two factors:
 (a) its resistance towards isomerization and decomposition reactions,
 and (b) its resistance towards deprotonation, which is related to the basicity of the parent molecule.

Cations of the less basic isomers of the di-, tri-, and tetramethylbenzenes are chemically unstable due to their tendency to isomerize to the more highly stabilized cations of m-xylene, mesitylene (1,3,5-trimethylbenzene) and isodurene (1,2,3,5-tetramethylbenzene) respectively. The rearrangements are fast, with rate constants ranging from 10^{-5} sec^{-1} to $3 \times 10^{-3} \text{ sec}^{-1}$ ²⁹. They all proceed by successive 1,2-hydrogen and 1,2-methyl shifts, with the methyl shifts as the rate determining steps. For example, the conversion of o-xylenium ions (10) to m-xylenium ions (3):

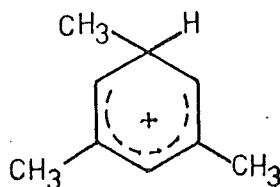


(10)



(3)

The variations in the rates of these reactions can be rationalized by considering the stabilities of the cations which occur as intermediates in the respective overall reactions. Mesitylenium ion for example, shows no evidence of intramolecular hydrogen shifts because of the low stability of the intermediate cation (11):



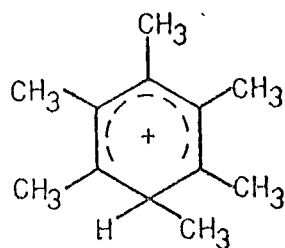
(11)

The result of fast, reversible intra- or intermolecular hydrogen exchange reactions is temperature-dependent broadening,

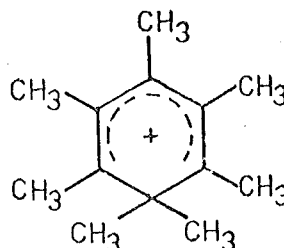
and in extreme cases the coalescence, of lines in the NMR spectra of arenonium ions. Intramolecular shifts normally take place between ring carbons of equal basicity, and may be distinguished from intermolecular exchange in two ways - (a) the rate of the intramolecular exchange is independent of the acidity of the solvent. (b) In the collapsed spectrum the hyperfine splittings due to coupling between the hydrogens taking part in the reaction and the other hydrogens in the molecule persist, though in a modified form if the reaction is intramolecular. An example of this is the hexamethylbenzenonium ion in HF-SbF_5 at -20° , where the coalesced methyl signal is split into a doublet by the exchanging proton which is itself split into a multiplet (theoretically nineteen lines) by the methyl groups.

These effects have allowed the occurrence of intramolecular hydrogen shifts to be established in the cations of several methylbenzenes^{7,29,30,31} and in a number of halogen-containing benzenonium ions^{32,33}. It was found that 1,3- and 1,4-hydrogen shifts do not occur in benzenonium ions, as evidenced by the lack of rapid intramolecular shifts in the cations of mesitylene and isodurene where the highly basic positions are separated from each other by very much less basic positions, and the stepwise process is practically blocked.

In benzenonium ions the 1,2-methyl shift is very much slower than the hydrogen shift. A direct comparison is provided by the hexamethylbenzenonium ion (12) and the heptamethylbenzenonium ion (13)



(12)



(13)

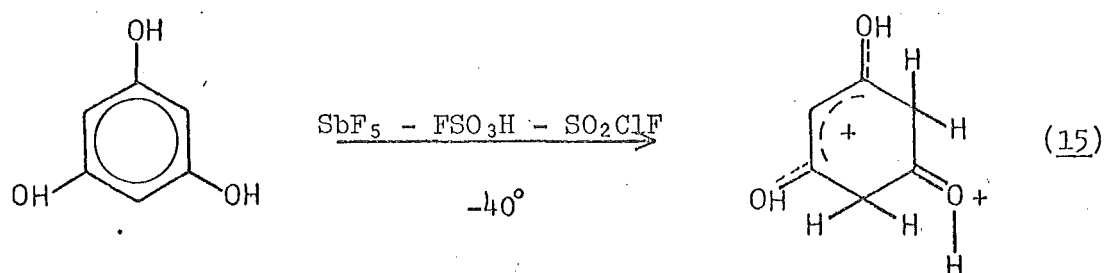
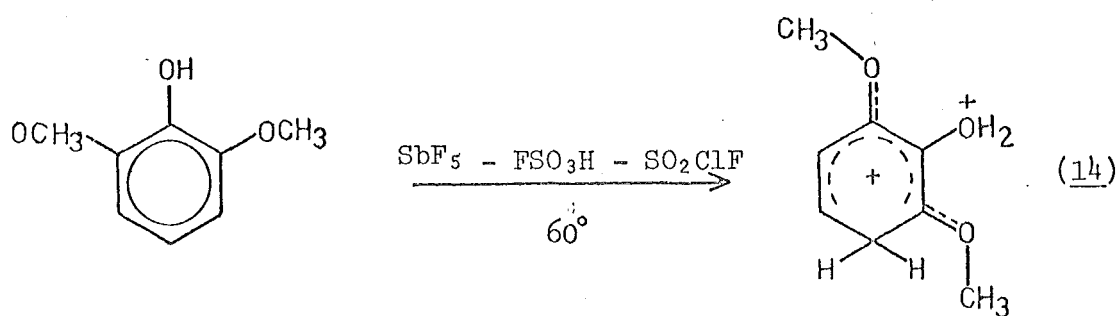
For (12)³¹, $k = 5 \times 10^{-4} \text{ sec}^{-1}$ at 0° , and for (13)³⁴ $k = 12.5 \text{ sec}^{-1}$ at 49° , the large difference in rate being entirely due to the difference in heat of activation. However like that of the hydrogen shift, the rate of the 1,2-methyl shift depends strongly on the structure of the carbonium ion.

The lifetime of an arenonium ion can also be shortened by intermolecular proton transfer when the acidity of the solvent is sufficiently low. This process will also cause line-broadening in the NMR spectrum. Proton exchange may occur (a) with unprotonated arene molecules, and (b) with solvent molecules or anions. Although type (a) appears to be accelerated in the case of methylbenzenes by the formation of cation-molecule complexes, the rate of intermolecular exchange may be considerably decreased by the use of stronger acid systems and lower temperatures.

As is to be expected from their stronger electron-releasing actions, hydroxyl and alkoxy substituents increase ^{the} basicity of the benzene ring much more than alkyl substituents. As a consequence, protonation of these more activated systems has been carried out in a wider variety of solvent systems than for the alkylbenzenes. Apart

from the superacid systems previously mentioned, much work has been done in concentrated aqueous H_2SO_4 and HClO_4 solutions^{13,35,36,37}.

It was quickly found that the favoured site for ring protonation was para to an oxygen substituent. The spectra of the conjugate acids of the polyalkoxybenzenes were simply interpreted on this basis, but a complication appeared with the stronger superacid media when di-cations were observed, with the second proton either residing on an oxygen substituent meta to the position of initial attack (14) or attacking the ring for the second time (15)^{36,38,39}.



Conflicting evidence was found as to the preference for protonation para to a hydroxyl or alkoxy substituent, this seeming to depend on acid strength. Hydroxyl substituents appear to be superior to alkoxy groups in stabilizing a cation in more dilute acids, but the reverse was the case in more concentrated acids^{36,37,39}.

The situation becomes more complex with phenol and anisole where although the oxygen substituent raises the basicity of the ring to such an extent that the carbon atom para to the substituent can compete successfully with the oxygen atom for the acidic proton it can only do so by a small margin.

The subtle interplay of several factors seems to determine whether oxygen or carbon protonation is observed. O-protonation tends to predominate at low temperatures while further substitution of the ring causes C-protonation to play a greater part. The strength of the acid system and the temperature-dependent rate of exchange of the proton on oxygen compared with the rate of exchange on carbon is important, particularly for NMR investigations where differences in these exchange rates will determine which type of protonation will be observed experimentally. O-protonated cations have been observed to exchange their protons much more readily than C-protonated cations⁴⁰.

To illustrate the sort of variation which is observed, it has been reported that in HF-BF₃ anisole protonates either on oxygen or the 4-position in ratios of 1:1.5 at -80° and 1:50 at 0°⁴⁰. In FSO₃H only ring protonation is observed^{7,8} in contrast to the results in HF. p-Methylanisole, too, exhibits interesting behaviour. In neat fluorosulphonic acid it has an O:C-protonation ratio of about 3.5:1, invariant with temperature. In FSO₃H-SbF₅ mixtures, the ratio becomes temperature dependent⁴¹.

Temperature dependence of the oxygen: carbon protonation ratio indicates differing heats of protonation at the two sites,

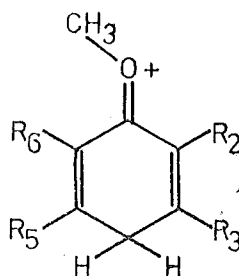
with O-protonation being more exothermic as it predominates at lower temperatures. It has been estimated⁴¹ that for *p*-methylanisole in 20% SbF₅-FSO₃H, O-protonation is favoured by 2900 J mol⁻¹ and in 33% SbF₅-FSO₃H by 18,800 J mol⁻¹. It is clear, then, that the thermodynamics of O- and C-protonation are quite similar and small changes in conditions may cause large changes in the ratio of O:C-protonation.

However, *p*-methylanisole in neat fluorosulphonic acid has a ratio of O:C-protonation which is unchanged over the range -40° to -80°¹¹, indicating that in this solvent the enthalpies of protonation on carbon and oxygen are the same. Thus the entropy of oxygen protonation must be more favourable, since more of the O-protonated ion is formed. This entropy difference suggests that not only are the two cations solvated differently (the starting material and anions formed must be identical), but also that more solvent organisation is required for the ring-protonated species. Since it has been found that a good hydrogen-bond acceptor tends to favour an O-protonated over a C-protonated species⁴² and also that hydrogen bonding is an important stabilizing factor for nitrogen and oxygen bases in fluorosulphonic acid⁴³, it is reasonable to deduce that solvation differences play an important part in determining the O:C-protonation ratio. Our knowledge of the nature of strong acids and of solvent-solute interactions will, however, have to improve enormously before the effects of such small energy changes can be rationalized with confidence.

Further alkyl substitution in phenol or anisole increases

the basicity to the extent that ring protonation becomes more favoured than oxygen protonation, and the acidic proton is captured by the para ring carbon. 3-Methylanisole, 2,5-dimethylanisole, and 3,5-dimethylanisole are ring protonated in HF-BF_3 ⁴⁰. However substitution of a methyl group para to the oxygen function may change the O-C-protonation pattern as the activating influence of the oxygen appears to be much less at the ortho position.

Other exceptions to para attack are due to the steric requirements of the methoxy group. Activation of the para position in the benzene ring will only occur if, in the cation, the methoxy group can be accommodated in the plane of the ring, because of the contribution of the resonance structure (16) to the stabilization of the positive charge generated.



(16)

In the case of 2,6-dimethylanisole [(16), $R_2 = R_6 = \text{CH}_3$, $R_3 = R_5 = \text{H}$] this is made sterically impossible by the o-methyl groups, so protonation occurs at oxygen only⁴⁰.

Another consequence of the coplanarity of the methoxy group and the ring is the detection of rotational isomers for protonated anisole derivatives. For anisole itself in HF below -10° , the

hydrogens at the 2- and 3- positions are non-equivalent to the 5- and 6- hydrogens due to the influence of the methoxy methyl⁴⁴. The same situation is observed for 3,5-dimethylanisole, with the difference that lower temperatures are needed to freeze out the rotational isomers, as the methyl substituents favour structures with the positive charge at the ring and the contribution of the quinonoid resonance structure is less. The rotational barrier is lower for the dimethylanisole, with $k = 10^2 \text{ sec}^{-1}$ at 40° for 3,5-dimethylanisole and at -15° for anisole⁴⁴. It appears that the hindered rotation takes place in the cations themselves rather than when the cations are temporarily converted to their conjugate bases, since at high temperatures the CH_2 signal in the NMR spectrum remains unchanged, and the coupling between the CH_2 protons and the ortho ring protons persists, indicating that at lower temperatures any deprotonation reaction must have been too slow to account for the high rate of rotational equilibrium.

The NMR spectra of hydroxy- and methoxybenzenonium ions are similar to those of the methylbenzene cations, but may be made more complex by the presence of two or three isomeric cations. The strong electron releasing effect of the methoxy group is clearly reflected by the chemical shifts of the ring protons and alkyl substituents, which are generally displaced to much higher field than in the corresponding hydrocarbons. The spin-spin couplings between various hydrogens in methoxybenzenonium ions are generally larger than in methylbenzenonium ions the coupling between ortho ring protons and CH_2 protons, for instance, being about 35cps in the former case compared with about 1cps in the latter.

Proton exchange is generally not the problem in the more basic phenols and anisoles that it is in the analogous methylbenzenes although as previous discussion has indicated, exchange rates may determine which cations are detectable experimentally in the less basic cases where oxygen protonation is a serious competitor. However as basicity increases and ring protonation predominates, exchange reactions assume lesser importance as exchange of carbon-protonating hydrogens is generally not sufficiently fast to give rise to significant line broadenings in the NMR spectrum.

The aim of this study was to look more closely at these more activated systems, particularly those with a substituent on the site of protonation. A great deal of work has already been done in the field of electrophilic substitution, of which protonation is just one example, but although there is a large mass of data available concerning the effects of ortho, meta, and para substituents on electrophilic attack, little data exists on the directing effects of substituents to ipso attack. By examining the protonation pattern in molecules which are sufficiently basic to allow attack at a substituted site, it was hoped to gain a better appreciation of the factors governing the site of electrophilic attack and the mechanisms of stabilizing the cations formed.

EXPERIMENTAL

Melting points are uncorrected. PMR spectra were recorded either on a Varian A60 or T60 spectrometer equipped with a variable temperature probe, CMR spectra on a Varian CFT20 NMR spectrometer, also equipped with a variable temperature probe. Accurate masses were determined on an A.E.I. MS902 high resolution mass spectrometer, and GLC analyses were performed on a Varian Aerograph 1200 gas chromatograph.

Alumina used in column chromatography was Spence grade H deactivated with 5% v/v or 10% v/v aqueous acetic acid. Silica gel used in chromatography was from Crosfield and Sons, England.

Materials.

Fluorosulphuric acid was obtained from two sources, Aldrich Chemical Company and Fluka A.G. It was distilled off sodium fluoride (1gm/100ml) under dry nitrogen before use. Nitronium tetrafluoroborate was obtained from K and K Laboratories Inc. and used without further purification.

Many of the phenols and naphthols used in this study are available commercially. The purity of these compounds was checked by melting point or GLC, and recrystallization or distillation was carried out if further purification proved necessary. The commercial samples used include 2,3-dimethylphenol, 2,6-dimethylphenol, 3,5-dimethylphenol,

β -naphthol (L. Light and Co.), 3,4-dimethylphenol (B.D.H.), 2,3,5-trimethylphenol, 3,4,5-trimethylphenol (Aldrich Chemical Co.), *p*-cresol, α -naphthol (Riedel-De Haën), 2,4,6-trimethylphenol, *o*-, *p*-nitrophenols (Fluka AG), 2,4,5-trimethylphenol (Columbia Organic Chemicals Co.), *m*-nitrophenol (Hopkin and Williams), 2,4-dimethylphenol (Koch-Light Laboratories).

In many cases the methyl ethers of the phenols and naphthols were required for study. These were prepared from the parent hydroxy compound by the method of Barger and Silberschmidt:⁴⁵ 0.11 moles of a phenol was melted in a flask, and with rapid stirring 8.2gm potassium hydroxide in 12cc water was run in at the rate of two drops per second. 20 seconds after this had started, 16cc of dimethylsulphate was started to run in at the same rate. External heating was soon stopped, and as soon as all the reagents had been run in (about 15 minutes), the reaction mixture was poured into a separating funnel and extracted with ether. The ether layer was washed with 10% sodium hydroxide, dried and evaporated, and the product distilled. The yield was nearly quantitative except for hindered (2,6-disubstituted) phenols, when it was about 50%.

2,3,4-Trimethylphenol.

(a) 2,3,4-Trimethylbromobenzene. 6.3ml of bromine in 35ml carbon tetrachloride was added over a two hour period to a stirred solution at -7° of 14gm 1,2,3-trimethylbenzene in 40ml carbon tetrachloride containing small amounts of iron powder and iodine. Stirring was continued for another hour at -7° and the mixture then left for two

hours as the temperature rose. Excess bromine was removed by treatments with 2N sodium hydroxide solution and water, and solvent removed at atmospheric pressure. Distillation gave 92% 2,3,4-trimethylbromobenzene⁴⁶, b.p. 108° at 15mm.

(b) 2,3,4-trimethylphenol⁴⁷. To a 500ml three-necked flask equipped with a stopcock on the bottom and carrying a reflux condenser, dropping funnel, stirrer, nitrogen inlet, and drying tube was added 10.3gm of methyl borate and 135ml of dry ether. The apparatus was flushed with dry nitrogen, and 66ml of a 1.5M solution of the Grignard reagent from 2,3,4-trimethylbromobenzene was added dropwise over a period of one hour while the contents of the flask was cooled to -80° and vigorously stirred. After the addition the reaction mixture was warmed to room temperature and 100ml of 10% hydrochloric acid slowly run in with stirring under nitrogen. The stirrer was stopped, and the lower aqueous phase was separated by using the stopcock in the bottom of the flask. After the ether layer had been washed twice more with water in this fashion, 66ml of 10% hydrogen peroxide was added slowly from the dropping funnel, with stirring, at such a rate as to maintain gentle reflux. After the addition the stirring was continued for 15 minutes and the layers separated as before. The ether layer was washed with 10% ferrous ammonium sulphate and the phenol extracted with two portions of 10% sodium hydroxide. The aqueous phase was then acidified, extracted with ether, and the product dried and distilled. The yield of 2,3,4-trimethylphenol was 2.7gm (20%) (m.p. 75-77°). (lit.⁴⁸ 76-77°). NMR δ 2.17 (s, 9H, CH_3), 3.77 (s, 1H, OH), 6.69 (m, 2H, C_5H , C_6H).

2,3,4,5-Tetramethylphenol.

(a) 1,2,3,4-Tetramethylbenzene was brominated by the method of Topsom and Vaughan⁴⁶ to give 98% 2,3,4,5-tetramethylbromobenzene.

(b) 2,3,4,5-Tetramethylbromobenzene was converted via the Grignard reagent to the phenol by Hawthorne's method⁴⁷. The yield was 5.5gm (49%), m.p. 82° (lit⁴⁹ 82°). NMR δ 2.08, (br.s, 12H, CH_3), 3.50 (s, 1H, OH), 6.25 (s, 1H, C_6H).

6-Nitro-3,4-dimethylphenol

(a) o-Xylene-4-acetate⁵⁰. 6.0gm of 3,4-xyleneol in 40ml 10% sodium hydroxide solution was put in a conical flask and 45gm of crushed ice was added. After the addition of 7.6ml acetic anhydride the flask was corked and shaken vigorously for about five minutes. The mixture was extracted with carbon tetrachloride, and the organic layer washed with saturated sodium bicarbonate and 10% sodium hydroxide solutions. The solvent was removed and the residue distilled, giving 7.6gm (94%) of 4-acetoxy-o-xylene, b.p. 130° at 20mm.

(b) 4-Nitro-3,4-dimethylcyclohexadienone. 5gms of 4-acetoxy-o-xylene was dissolved in 7.5ml acetic anhydride and the solution cooled to 0°. 1.5ml of redistilled nitric acid in 7.5ml acetic anhydride was added with stirring over a 30 minute period at 0°, and the reaction then stirred for another hour at this temperature. The reaction mixture was then cooled to -60°, and the dienone crystallized out. It was filtered off and made to decompose immediately.

(c) 6-Nitro-3,4-dimethylphenol. The dienone prepared above

was dissolved in glacial acetic acid and allowed to stand for two days. Removal of the acid yielded a 1:1 mixture of 6-nitro and 2-nitro-3,4-dimethylphenol. Column chromatography on silica gave 38% 6-nitro-3,4-dimethylphenol, m.p. 86-87° (lit.⁵¹87°). NMR δ 2.25 (s, 3H, C₄CH₃), 2.31 (s, 3H, C₃CH₃) 5.07 (s, 1H, OH), 6.97 (s, 1H, C₂H), 7.87 (s, 1H, C₅H)

6-Bromo-3,4-dimethylphenol.

11gm of bromine was slowly added with cooling and stirring to a solution of 8gms of 3,4-xylenol in 33cc glacial acetic acid, and the resulting mixture allowed to stand at room temperature for twelve hours. After the acetic acid had been removed under vacuum, the residue was taken up in benzene and washed thoroughly with water. The solvent was then stripped off and the product recrystallized from water, giving 12gm (66%) 6-bromo-3,4-dimethylphenol, m.p. 77-79° (lit.⁵²80°). NMR δ 2.33 (s, 6H, CH), 5.25 (s, 1H, OH), 6.28 (s, 1H, C₂H), 7.20 (s, 1H, C₅H).

4,5-Dimethoxy-o-xylene.

(a) 1,2-Dimethoxy-4,5-dichlorobenzene.⁵³ Sulphuryl chloride (112cc) was added over one hour to stirred o-dimethoxybenzene (80gm) at 15-20°, stirring being continued at this temperature for an hour and then at 75-80° for two further hours. The excess of chloride was removed with a water pump and the residue, after being washed with cold petroleum ether, was recrystallized from ethanol. The yield was 70gm (59%), m.p. 83° (lit.⁵³83.5°).

(b) 4,5-Dimethoxy-o-xylene.⁵⁴ Methyl lithium⁵⁵ from 50cc methyl iodide and 13gm lithium was stirred with 450^{ml} of ether at 0°, and 68gm of 1,2dimethoxy-4,5-dichlorobenzene added to it over a 45 minute period.

The resulting suspension was stirred at 0° for an hour, and then refluxed for three hours. After cooling, the mixture was decomposed at 0° with 300cc water, and acidified with 10% hydrochloric acid. The ethereal phase was separated, washed with water, and dried, removal of the solvent giving a dark residue which was distilled to give a colourless oil. Recrystallization from petroleum ether gave 33gm (60%) of 4,5-dimethoxy-o-xylene, m.p. 40-43° (lit.⁵⁶ 43.5°). NMR δ 2.14(s, 6H, CH₃), 3.72(s, 6H, OCH₃), 6.54(s, 2H, C₃H, C₆H).

2-Methyl-4-ethylphenol.

(a) 3-Methyl-4-hydroxyacetophenone. Aluminium chloride (21gm), nitrobenzene (120ml), and o-cresyl/acetate (21gm) were held at room temperature for 48 hours, then treated with 75ml water and 110ml 10% hydrochloric acid. The mixture was extracted with 150ml benzene, the extract washed with water and added to 200ml 5% sodium hydroxide. The aqueous layer was washed with ether and then acidified, the oil which separated being extracted with ether, dried and evaporated. The crude product was recrystallized from aqueous ethanol to give 4.9gm (22%) of 3-methyl-4-hydroxyacetophenone, m.p. 107-110° (lit.⁵⁷ 110°)

(b) 2-Methyl-4-ethylphenol. 1.1gm of 3-methyl-4-hydroxyacetophenone in 25ml acetic acid was added to 10ml 33% hydrochloric acid and 1.5gm amalgamated zinc and refluxed for 24 hours. The mixture was poured into 50ml water and extracted with benzene, the organic layer being washed with sodium carbonate solution before being dried and evaporated. The yield was 90% of crude product which was purified by chromatography on silica.⁵⁸ NMR δ 1.15 (t, 3H, CH₂CH₃, J=7H_Z), 2.15(s, 3H, CH₃),

2.50(q, 2H, CH_2CH_3), 5.60(s, 1H, OH), 6.63(m, 3H, C_3H , C_5H , C_6H).

3-Methyl-4-ethylphenol.

(a) 2-Methyl-4-hydroxyacetophenone. Aluminium chloride (14.5gm), nitrobenzene (90ml), and *m*-cresylacetate (12.5gm) were held at room temperature for 48 hours, then treated with 50ml water and 75ml 10% hydrochloric acid. The mixture was extracted with 100ml benzene, the extract washed with water, and after the addition of 200ml 1N sodium hydroxide the whole mixture was steam distilled. The residual solution was clarified with carbon and acidified with hydrochloric acid to give 4.4gm (35%) of crude product on extraction with ether. Further purification was effected by column chromatography on silica. M.p. 127-128° (lit.⁵⁹ 129°)

(b) 1.1gm of 2-methyl-4-hydroxyacetophenone in 25ml acetic acid was added to 10ml 33% hydrochloric acid and 1.5gm amalgamated zinc and refluxed for 24 hours. The mixture was then poured into 50ml water and the product extracted with benzene, the benzene solution being washed with sodium carbonate solution and water before being dried and evaporated. The crude reaction mixture contained 90% 3-methyl-4-ethylphenol which was purified by column chromatography on silica.⁵⁸ NMR δ 1.17(t, 3H, CH_2CH_3 , $J=7\text{Hz}$), 2.18(s, 3H, CH_3), 2.52(q, 2H, CH_2CH_3), 4.32(s, 1H, OH), 6.70(m, 3H, C_2H , C_5H , C_6H). Found for $\text{C}_9\text{H}_{12}\text{O}$, $M^+=136.088517$, required $M^+=136.088803$.

3-Ethyl-4-methylphenol

(a) 3,4-Dimethyl-4-trichloromethyl-2,5-cyclohexadienone(I).⁶⁰
A solution of 61gm (0.5mole) of 3,4-dimethylphenol in 300ml carbon

tetrachloride was added over 30 minutes to a stirred slurry of 133gm anhydrous aluminium chloride in 300ml carbon tetrachloride, keeping the reaction mixture at a temperature of 5-20° while a slow stream of dry nitrogen swept the hydrogen chloride formed into traps containing measured amounts of sodium hydroxide solution. After two hours 0.4 moles of acid had been evolved and the reaction mixture was poured on 1.5l of ice containing 100ml concentrated hydrochloric acid. After thorough (30 minutes) decomposition of the reaction complex (stirring) the organic phase was collected, washed with water and 10% sodium hydroxide, and finally with saturated sodium chloride solution. The organic layer was then dried, the solvents removed and the products vacuum distilled. The fraction boiling near 135° (1mm) was crystallized from petroleum ether to yield the product as colourless needles m.p. 60-61° in 60% yield.

(b) 4-Methyl-3-(β,β,β -trichloroethyl) phenol (II).⁶¹ 50gm of I in 300ml acetic anhydride containing 1ml of concentrated sulphuric acid was held at reflux for five hours. After the removal of most of the acetic anhydride under reduced pressure, crude product (as the acetate) was obtained by distillation as an oil b.p. 134-136° (11mm) which soon crystallized.

Hydrolysis of the acetate in aqueous methanol containing about two equivalents of potassium hydroxide by heating to reflux for several minutes yielded after acidification 4-methyl-3-(β,β,β -trichloroethyl) phenol m.p. 111-112° (petroleum ether).

(c) 3-(β,β -dichlorovinyl)-4-methylphenol (III).⁶¹ On heating a solution of II in excess (about 2.5-3ml per gram) piperidine at 75° for ten hours, III was obtained in over 90% yield by pouring the reaction mixture into excess dilute hydrochloric acid. The product

was purified by distillation (b.p. 110° at 1mm) and by crystallization from petroleum ether (m.p. $89-90^{\circ}$).

(d) 3-ethyl-4-methylphenol. A solution of 5gm III in 100ml methanol was reduced over 0.5gm platinic oxide catalyst with a hydrogen pressure of 300kPa. The reduction proceeded smoothly to yield 2.5gm (75%) of product m.p. $35-36^{\circ}$ from petroleum ether. NMR δ 1.07 (t, 3H, CH_2CH_3 , $J=7\text{Hz}$), 2.12(s, 3H, CH_3), 2.44(q, 2H, CH_2CH_3), 6.10(s, 1H, OH), 6.60(m, 3H, C_2H , C_5H , C_6H). Found for $\text{C}_9\text{H}_{12}\text{O}$, $M^+ = 136.088648$, required $M^+ = 136.088803$.

3,4-Diethylphenol

(a) m-Bromoacetophenone.⁶² In a one-litre three-necked round-bottomed flask equipped with a condenser, dropping funnel and stirrer was placed 112gm anhydrous aluminium chloride. Acetophenone (40.4gm) was added slowly with vigorous stirring over a ten minute period, and to the resulting molten mass 64.4gm bromine was added dropwise with stirring over fifteen minutes. About one hour after the completion of this addition the stirred mass solidified. The solid complex was carefully dropped in portions into a two litre beaker containing crushed ice and 100ml concentrated hydrochloric acid, while the ice was hand-stirred vigorously. The dark oil which formed was extracted with ether, washed with water and sodium bicarbonate, dried and distilled. The yield was 53gm, b.p. $100-103^{\circ}$ at 6mm.

(b) m-Bromo-ethylbenzene.⁶³ To amalgamated zinc formed from 100gm zinc powder and 10gm mercuric chloride was added 75cc water, 175cc concentrated hydrochloric acid, 100cc toluene, and 50gm m-bromoacetophenone. The mixture was refluxed for twenty-four hours

with three 50cc portions of concentrated hydrochloric acid being added at six hour intervals. The organic layer was then separated, washed, dried, and distilled. The yield of product was 20gm, b.p. 80-84° at 6mm.

(c) m-Ethylphenol. The Grignard reagent from m-bromo-ethylbenzene was converted to the phenol via the method of Hawthorne⁴⁷ which has been previously described. The yield was 4gm of m-ethylphenol b.p. 80° at 5mm (lit.⁶⁴ 95° at 10mm).

(d) 3-Ethyl-4-acetylphenol.⁶⁵ m-Ethylphenol was converted to the acetate by treatment with acetic anhydride in 10% sodium hydroxide solution.⁵⁰ 6gm of anhydrous aluminium chloride was then gradually added to 5gm m-ethylphenylacetate in 12.5gm nitrobenzene maintained at 0°. After five days the mixture was decomposed with ice-water and steam distilled. The para isomer did not distill and crystallized in the distillation flask. The yield was 2gm, m.p. 101-102°.

(e) 3,4-Diethylphenol. 3-Ethyl-4-acetylphenol was reduced with amalgamated zinc and hydrochloric acid in the manner previously described.⁵⁸ The yield was 60% of diethylphenol, b.p. 106° at 5mm.⁶⁴ NMR δ 1.13(t, 6H, CH₂CH₃, J=7Hz), 2.53(q, 4H, CH₂CH₃), 5.13(s, 1H, OH), 6.70(m, 3H, C₂H, C₅H, C₆H). Required for C₁₀H₁₄O, M⁺=150.104455, found M⁺=150.104433.

2,4-Dimethyl-5-ethylphenol.

(a) 2,4-Dimethylacetophenone.⁶⁶ A solution of 0.5moles m-xylene in 200ml carbon disulphide was placed in a three-necked flask equipped with a mechanical stirrer, dropping funnel, and reflux condenser. To this was added 1.1mole (145.7gm) of powdered aluminium

chloride, and then with rapid stirring, 0.5mole (51gm) of acetic anhydride was added slowly. This took about fifteen minutes during which time the temperature reached 47° (b.p. CS_2) and hydrogen chloride was evolved. After the addition was complete, the mixture was stirred and heated on a water bath for half an hour, after which time the gas evolution had almost stopped. The reaction mixture was cooled to room temperature, and decomposed by pouring into ice and water. The carbon disulphide was allowed to evaporate during the decomposition. The mixture was then cooled and extracted with ether, the ether layer washed with water, 10% sodium hydroxide solution, and then again with water. After drying and evaporation of the solvent, the product was distilled. The yield was 83%, b.p. 92° (5mm).

(b) 4-Ethyl-m-xylene. 2,4-dimethylacetophenone was reduced with amalgamated zinc and hydrochloric acid in the usual way.⁵⁸ The yield was 65%, b.p. 58° (5mm).

(c) 2,4-Dimethyl-5-ethylbromobenzene. Bromination of 4-ethyl-m-xylene was carried out by the method of Topsom and Vaughan.⁴⁶ The yield was 90%, b.p. 104° (5mm).

(d) 2,4-Dimethyl-5-ethylphenol. The Grignard reagent from 2,4-dimethyl-5-ethylbromobenzene was converted to the phenol by Hawthorne's method,⁴⁷ yield 15%. NMR δ 1.10(t, 3H, CH_2CH_3 , $J=8\text{Hz}$) 2.10(s, 6H, CH_3), 2.48(q, 2H, CH_2CH_3), 4.18(s, 1H, OH), 6.40(s, 1H, C_3H), 6.73(s, 1H, C_6H). The product was then converted⁴⁵ to the methoxy derivative, NMR δ 1.17(t, 3H, CH_2CH_3 , $J=8\text{Hz}$), 2.10(s, 3H, CH_3), 2.52(q, 2H, CH_2CH_3), 3.73(s, 3H, OCH_3), 6.47(s, 1H, C_3H), 6.73(s, 1H, C_6H). Required for $\text{C}_{11}\text{H}_{16}\text{O}$, $M^+=164.120109$, found $M^+=164.119774$.

2,5-Dimethyl-4-ethylphenol.

(a) 4-Acetyl-2,5-dimethylphenol.⁶⁷ 21.0gm of 2,5-dimethylphenylacetate in 120ml of dry nitrobenzene was added slowly, with cooling, to 21gm of aluminium chloride in 80ml nitrobenzene. The mixture was then allowed to stand at room temperature for three days, after which time it was carefully added to 110ml of 10% hydrochloric acid and 75ml water. After extraction with 140ml benzene, the phenolic products were extracted from the organic layer by treatment with two 100ml portions of 5% sodium hydroxide. The combined alkaline extracts were then acidified, and the precipitate formed was taken up in ether. Evaporation of the solvent yielded 9.0gm of 4-acetyl-2,5-dimethylphenol m.p. 125-127° (lit.⁶⁷ 130°).

(b) 4-Acetyl-2,5-dimethylphenol was reduced with amalgamated zinc and hydrochloric acid in the usual way.⁵⁸ After purification by column chromatography on silica, the yield of 2,5-dimethyl-4-ethylphenol was 5.8gm (70%). NMR δ 1.10(t, 3H, CH₂CH₃, J=7Hz), 2.12(s, 6H, CH₃), 2.45(q, 2H, CH₂CH₃), 4.73(s, 1H, OH), 6.33(s, 1H, C₃H), 6.73(s, 1H, C₆H). Methylation by the method of Barger and Silberschmidt⁴⁵ gave 2,5-dimethyl-4-ethylanisole in quantitative yield. NMR δ 1.18(t, 3H, CH₂CH₃, J=7Hz), 2.05(s, 3H, C₅CH₃), 2.17(s, 3H, C₂CH₃), 2.40(q, 2H, CH₂CH₃), 3.67(s, 3H, OCH₃), 6.39(s, 1H, C₃H), 6.70(s, 1H, C₆H). Required for C₁₁H₁₆O, M⁺=164.120109, found M⁺=164.119836.

2,5-Dimethyl-4-methoxybenzylalcohol.

(a) 2,5-Dimethyl-4-formylanisole.⁶⁸ To 50gm of 2,5-dimethylanisole and 37gm dimethylformamide, 87gm phosphorus oxychloride was added portionwise and the mixture heated for three hours on a steam bath. It was then shaken with concentrated sodium acetate and

the aldehyde taken up in benzene. The benzene solution was washed with 6N hydrochloric acid and water, and, after drying, evaporation of the solvent left a residue containing a 50/50 mixture of starting material and the product aldehyde. The aldehyde was extracted as the bisulphite adduct by stirring vigorously for several hours with a saturated sodium bisulphite solution. The solid was filtered off, washed with a little ether, and dissolved in water. The addition of an aqueous sodium carbonate solution decomposed the adduct, allowing the aldehyde to be extracted in 40% yield.

(b) 2,5-Dimethyl-4-methoxybenzylalcohol.⁶⁹ 0.9gm of lithium aluminium hydride was suspended in dry ether in a flask fitted with a reflux condenser, dropping funnel, drying tube, and nitrogen inlet. A solution of 5gm 2,5-dimethyl-4-formylanisole also in ether was added at such a rate as to maintain gentle reflux. After the addition was complete, the reflux was continued for one hour before the mixture was poured cautiously into cold water. The product was extracted with ether, dried and evaporated, and the white solid recrystallized from petroleum ether. The yield was 3.1gm (61%) m.p. 53-55° NMR δ 1.22 (s, 1H, OH), 2.13 (s, 3H, C₂CH₃), 2.30 (s, 3H, C₅CH₃), 4.45 (s, 2H, CH₂OH), 6.50 (s, 1H, C₃H), 6.92 (s, 1H, C₆H). Required for C₁₀H₁₄O₂, M⁺=166.099369, found M⁺=166.099167.

2,5-Dimethyl-4-chloro^{METHYL}anisole.⁷⁰

1.5gm of 2,5-dimethyl-4-methoxybenzylalcohol was dissolved in 2.5cc dry benzene, and to it was added 1.5gm thionyl chloride and a trace of pyridine in 1cc benzene. The mixture was heated on a steam bath for an hour, and after cooling ice-water was added. Extraction gave 1.2gm (72%) of 2,5-dimethyl-4-chloromethylanisole, which was

separated from any residual traces of benzene by column chromatography.

NMR δ 2.08(s, 3H, C_2CH_3), 2.44(s, 3H, C_5CH_3), 3.84(s, 3H, OCH_3), 4.57(s, 2H, CH_2Cl), 6.60(s, 1H, C_3H), 7.02(s, 1H, C_6H). Required for $\text{C}_{10}\text{H}_{13}\text{OCl}^{35}$, $M^+ = 184.065630$, found $M^+ = 184.06$

4-Methyl-1-Naphthol.

(a) 1-Methyl-4-bromonaphthalene. 1-Methylnaphthalene was brominated by the method of Topsom and Vaughan⁴⁶ giving an 80% yield of the 4-bromo compound, b.p. 118° at 2mm (lit.⁷¹ 146° at 8mm)

(b) 4-Methyl-1-naphthol. 1-Methyl-4-bromonaphthalene was converted via the Grignard reagent to the naphthol, using Hawthorne's method.⁴⁷ The yield was 18% of white crystals, m.p. $82-84^\circ$ (lit.⁷² $83-84^\circ$). NMR δ 2.52(s, 3H, CH_3), 2.25(s, 1H, OH), 6.57(d, 1H, C_3H , $J=7\text{Hz}$), 7.03(d, 1H, C_2H , $J=7\text{Hz}$), 7.1-8.4(m, 4H, C_5H , C_6H , C_7H , C_8H).

1-Methyl-2-naphthol.

This was obtained from a sample prepared by Dr K.E. Richards by the method of Buu-Hoi and Lavit,⁷⁸ m.p. 110° .

3,4-Dimethyl-1-naphthol.

(a) 1,2-Dimethyl-4-bromonaphthalene. 1,2-Dimethylnaphthalene was brominated by the method of Topsom and Vaughan,⁴⁶ giving 83% yield of the 4-bromo compound, b.p. $156-159^\circ$ at 3mm (lit.⁷³ $190-195^\circ$ at 14mm).

(b) 3,4-Dimethyl-1-naphthol. 1,2-Dimethyl-4-bromonaphthalene was converted via the Grignard reagent to the naphthol using Hawthorne's method.⁴⁷ The yield was 27%, m.p. $121-122^\circ$ (lit.⁷⁴ $121.5-123^\circ$).

NMR δ 2.38(s, 3H, C₄CH₃), 2.50(s, 3H, C₃CH₃), 5.10(s, 1H, OH), 6.62(s, 1H, C₂H), 7.20-8.33(m, 4H, C_{5,6,7,8}H). Required for C₁₂H₁₂O, M⁺=172.088809, found M⁺=172.089089.

4,5-Dimethyl-1-naphthol

(a) 1,8-Bishydroxymethylnaphthalene.⁷⁵ A suspension of naphthalic anhydride (100g) in benzene (250ml) was added during two hours to a stirred solution of lithium aluminium hydride (50g) in ether (1l) and benzene (200ml). Stirring and refluxing was continued for a further three hours and most of the ether was then distilled off. The excess of metal hydride was destroyed by dropwise addition of ethyl acetate. Addition of concentrated potassium hydroxide solution (50ml) gave a white precipitate, and the liquid was then decanted off and the solid extracted with benzene (2×500ml) containing ether (50ml). The volume of the combined extracts was reduced to 250ml, ethanol (250ml) was added, and the solution was evaporated to about 200ml. 10% aqueous sulphuric acid was added and the precipitated dialcohol was filtered off, washed with water and dried. The yield was 62g (65.5%) m.p. 155°

(b) 1,8-Dimethylnaphthalene.⁷⁵ 60g Phosphorus tribromide in 200ml ether was added over two hours to a stirred solution of 1,8-bishydroxymethylnaphthalene (60g) in 1l benzene and 400ml ether. The mixture was refluxed for one hour and poured on 2kg crushed ice. The organic layer was washed with cold saturated sodium bicarbonate solution and water, dried, and most of the solvent removed. The solution remaining was added over two hours to a stirred solution of lithium aluminium hydride (20g) in 2l ether, and the mixture was refluxed for three hours. The excess of metal hydride was destroyed with ethyl acetate, and an excess of concentrated potassium hydroxide solution was added. The

organic layer was decanted and the residue was washed with 3x400ml of a 10:1 benzene:ether mixture. The combined organic extracts were washed with water, dried, and the solution distilled almost to dryness. The residue was taken up in ethanol, and on cooling the hydrocarbon precipitated. Recrystallization from ethanol yielded 38gm (76%) m.p. 60-62°.

(c) 1,8-Dimethyl-4-bromonaphthalene. 1,8-Dimethylnaphthalene was brominated by the method of Topsom and Vaughan⁴⁶ giving a 65% yield of 1,8-dimethyl-4-bromonaphthalene b.p. 190-195° at 20mm.

(d) 4,5-Dimethyl-1-naphthol. 1,8-Dimethyl-4-bromonaphthalene was converted via the Grignard reagent to the naphthol by Hawthorne's method.⁴⁷ The yield was 27% of white crystals, m.p. 120-122°. NMR δ 2.83(s, 3H, C₅CH₃), 2.90(s, 3H, C₄CH₃), 4.87(s, 1H, OH), 6.67(d, 1H, C₃H, J=8Hz), 7.09(d, 1H, C₂H, J=8Hz), 7.33(m, 2H, C_{6,7}H), 8.15(m, 1H, C₈H). Required for C₁₂H₁₂O, M⁺=172.08881, found M⁺=172.08875.

Preparation of Cations.

Fluorosulphuric acid (0.5ml) was placed in an NMR tube and cooled to -78°. The phenol (50mg) was added gradually with shaking and stirring until solution was complete.

Electrophiles other than H⁺.

Two attempts, both unsuccessful, were made with different electrophiles to produce cations analagous to those obtained from

protonation in fluorosulphuric acid.

Ipso attack by nitronium ions has been known for some years⁷⁶ and as the initial species formed by such attack must be a cation, an attempt was made to detect the ion by NMR. The source of nitronium ions used was nitronium tetrafluoroborate; the nitrating solution was made up by dissolving the nitronium salt in a minimum volume of fluorosulphuric acid at -78° and diluting to the required volume with sulphur dioxide. The phenol or hydrocarbon substrate was also dissolved in sulphur dioxide and the two solutions carefully mixed at -78° with rapid stirring before a sample was withdrawn for study.

Methylphenols were studied in this solvent system at -50° , and appeared to undergo one of two reactions: the product was either one of ring nitration or a cation resulting from protonation of the parent phenol. There was no evidence of a cation derived from attack by NO_2^{+} . The methylbenzenes, being less basic, gave only the products of ring nitration, as their conjugate acids exchange protons with the solvent much more quickly than the conjugate acids of the methylphenols. It appears that the cations resulting from ipso attack by NO_2^{+} are too short-lived to be detected by this method, and attack at an unsubstituted site quickly produces nitrobenzenes by an irreversible process.

The other electrophile used in an attempt to generate long-lived cations was cationic iodine. Deactivated molecules have been polyiodinated by solutions of iodine in oleum or concentrated sulphuric acid where the electrophile is probably I_2^{+} ⁷⁷ but these solvents are unsuitable for NMR studies, particularly at low temperatures where viscosity is a problem. Gillespie and Milne⁷⁸ have shown that the same electrophile is formed when iodine is oxidised by $\text{K}_2\text{S}_2\text{O}_8$ in

fluorosulphuric acid; however this mixture also became very viscous when mixed with an organic base at low temperatures. This difficulty was overcome by dilution with liquid SO_2 , but the examination of hexamethylbenzene and a number of phenols in this solvent system between -20° and -60° gave no evidence of ring attack. On this basis cationic iodine appears insufficiently reactive to form long-lived σ -complexes.

RESULTS:

The cations produced by protonation of the methyl-substituted phenols in FSO_3H were identified by their low temperature NMR spectra. The phenols which are unsubstituted in the 4-position were all protonated para to the hydroxyl group when dissolved in FSO_3H . The NMR spectra of these cations (Table 2) are completely consistent with the structures indicated and no other cations could be detected. The assignment of the resonances was made by considering their multiplicity and integration, together with the changes occurring in the spectra as the substitution pattern of the cation was altered.

The NMR spectra of cations derived from phenols with a para-methyl substituent are usually more complex than can be accounted for on the basis of protonation at a single site. The presence of a cation resulting from para protonation was shown by a high field doublet (c.a. $\delta 1.6$) and a quartet (c.a. $\delta 3.9$) characteristic of 4-methyl and 4-methine protons respectively. The other resonances of these para protonated cations are quite in accord with their proposed structures.

Cations resulting from proton attachment at an ortho position are also present in FSO_3H solutions of 4-substituted phenols. The NMR spectra show the presence of methylene groups which could not be produced by protonation meta to the hydroxyl group as its electron-donating properties would then be reduced, and a considerable down-field shift of all the resonances would be expected. Similar conclusions regarding the structures of these ions have been reached by Childs.⁷⁹

The least activated phenols sometimes give rise to a third type of

cation, with the proton added to the oxygen. This type of ion can be recognised by its characteristically broad NMR spectrum, without the resonances or couplings associated with the ring protonated ions.

Some confirmation of the assignments proposed is found in the observation that the chemical shifts for hydrogen and methyl fall into clearly discernable patterns. For para protonated species, for example, protons at positions 2 or 6 give rise to signals in the $\delta 7.0 - 7.25$ region, whereas those at the 3-position give signals at $\delta 8.15 - 8.50$. Methyl substituents at positions 2 or 6 give signals in the $\delta 2.17 - 2.40$ region while those at positions 3 or 5 appear at $\delta 2.50 - 2.60$. Protons at C_4 show two ranges, $\delta 4.10 - 4.25$ and $\delta 3.65 - 4.10$ depending on whether the other 4-substituent is hydrogen or methyl.

A similar situation is found for the ortho protonated species. The methylene group gives rise to signals in the $\delta 4.20 - 4.40$ region, C_2 protons at $\delta 7.00 - 7.20$ as in the para protonated species. Methyls at positions 2 and 4 are seen in the region $\delta 2.20 - 2.40$, with C_3 methyls at $\delta 2.70 - 2.80$.

Carbon magnetic resonance spectra of the cations are consistent with the structures proposed on the basis of the proton magnetic resonance spectra, the signals being assigned from their relative intensities and the expected charge distribution. C_1 , C_3 , and C_5 have their resonances at markedly lower field than the rest of the ring carbons, showing that the main centres of positive charge are ortho and para to the site of attack, as calculated by the Molecular Orbital Method. Variations in chemical shift within these two groups is generally small except when

substituted and unsubstituted ring carbons are compared; it is known⁸⁰ that for the $^{13}\text{C}_{\text{sp}^3}\text{-R}$ fragment the transition from $\text{R} = \text{CH}_3$ to $\text{R} = \text{H}$ is accompanied by an upfield shift of the ^{13}C signal by 7-10 ppm, and the magnitude of the effect seems slightly greater for these sp^2 carbons. As expected, the protonated carbons appear to carry little positive charge with the chemical shifts of CH_2 or CHCH_3 being between 40 and 50 ppm (downfield from TMS), close to those of the usual aliphatic CH_2 groups (27-32 ppm⁸¹).

The PMR spectra of protonated ethylphenols are very similar to those of their methyl analogs and were simply assigned on this basis, but the spectra of the protonated naphthols are rather more complex because of the presence of the second aromatic ring. Fortunately, however, no oxonium ions are formed, so each naphthol gives rise to no more than two isomeric ions, resulting from attack ortho or para to the hydroxyl group. These ions were easily identified as the PMR spectra of the protonated ring display the same features shown by the protonated phenols; those protons ortho and para to the site of attack have their resonances downfield from those in meta positions, and both the ring and the methylene or methine protons have chemical shifts comparable with those found in single ring systems.

(a) Methylphenols

Table 1. Percentage of Protonation at each site*†

Phenol	Oxygen	C ₂	C ₃ (C ₅)	C ₄	C ₆
4-methyl	90	9		1	‡
2,3-dimethyl				100	
2,4-dimethyl	65			6	29
2,6-dimethyl				100	
3,4-dimethyl				15	85
3,5-dimethyl				100	
2,3,5-trimethyl				100	
2,4,5-trimethyl				83	17
2,3,4-trimethyl				20	80
3,4,5-trimethyl		50		50	‡
2,3,4,5-tetramethyl				96	4

* Solvent : FSO₃H.

† The numbering system of the parent compound is retained in the cation here and in all succeeding tables.

‡ The 2-and 6-positions are equivalent.

Table 2. P.M.R. Data for Para-Protonated Species in FSO_3H^* .

Parent Phenol	C_2/C_6		C_3/C_5		C_4		Coupling
	Me	H	Me	H	Me	H	
4-methyl	-	?	-	?	1.57d	?	$J=7\text{Hz}$
2,3-dimethyl	2.28	7.32d	2.62	8.40d	-	4.25	$J_{5,6}=9.5\text{Hz}$
2,4-dimethyl	2.33	?	-	?	1.58d	4.10q	$J_{\text{Me,H}}=7\text{Hz}$
2,6-dimethyl	2.40	-	-	8.46	-	4.25	
3,4-dimethyl	-	?	2.66	8.26	1.62d	3.88q	$J_{\text{Me,H}}=7.5\text{Hz}$
3,5-dimethyl	-	7.07	2.58	-	-	4.10	
2,3,5-trimethyl	2.24	7.07	2.52	-	-	4.12	
2,4,5-trimethyl	2.29	7.15	2.62	8.15	1.65d	3.84q	$J_{\text{Me,H}}=7.5\text{Hz}$
2,3,4-trimethyl	2.31	7.25d	2.60	8.36d	1.65d	3.92q	$J_{\text{Me,H}}=8\text{Hz}$ $J_{5,6}=10\text{Hz}$
3,4,5-trimethyl	-	7.02	2.60	-	1.69d	3.76q	$J_{\text{Me,H}}=7.5\text{Hz}$
2,3,4,5-tetramethyl	2.23	7.01	2.56	-	1.66d	3.76q	$J_{\text{Me,H}}=7.5\text{Hz}$

*Chemical shifts measured relative to $(\text{CH}_3)_4\text{N}^+$ as an internal reference and converted to δ_{TMS} values by using $\delta_{\text{TMS}} = -3.20$ for the reference ion. d = doublet q = quartet.

Table 3. P.M.R. Data for Ortho-Protonated Species in FSO_3H^*

Parent Phenol	C ₂		C ₃		C ₄		C ₅		C ₆	
	Me	H	Me	H	Me	H	Me	H	Me	H
4-methyl	-	?	-	?	?	-	-	?	-	4.36
2,4-dimethyl	2.33	-	-	8.34	2.33	-	-	7.10	-	4.25
3,4-dimethyl	-	7.18	2.76	-	2.34	-	-	7.44	-	4.28
2,4,5-trimethyl	2.40	-	-	8.44	2.40	-	?	-	-	4.35
2,3,4-trimethyl	2.31	-	2.72	-	2.31	-	-	7.30	-	4.25
3,4,5-trimethyl	-	7.02	2.74	-	2.35	-	2.47	-	-	4.25
2,3,4,5-tetramethyl	?	-	2.56	-	2.23	-	?	-	-	4.19

*In ppm from TMS using $(\text{CH}_3)_4\text{N}^+$ as an internal standard.

Table 4. P.M.R. Data for Oxonium Ions in FSO_3H^*

Parent Phenol	C ₂ /C ₆		C ₃ /C ₅		C ₄	
	Me	H	Me	H	Me	H
4-methyl	-	7.35	-	7.35	2.38	-
2,4-dimethyl	2.40	7.30	-	7.30	2.40	-

*In ppm from TMS using $(\text{CH}_3)_4\text{N}^+$ as internal standard.

Table 5. ^{13}C .M.R. Data for Para-Protonated Species in FSO_3H^* .

Parent Phenol	Ring Carbons						Methyl Positions					
	C_1	C_2	C_3	C_4	C_5	C_6	C_2	C_3	C_4	C_5	C_6	
2,3-Dimethyl	188.6	132.1	187.5	45.3	168.1	124.6	10.4	23.2				
2,4-Dimethyl	191.1	?	169.5	45.6	175.6	?	16.2 [†]		15.8 [†]			
2,6-Dimethyl	191.1	134.4	169.5	40.5	169.5	134.4	15.0					15.0
3,5-Dimethyl	189.7	122.0	188.3	42.3	188.3	122.0		24.7		24.7		
2,3,5-Trimethyl	188.2	130.2	185.8	48.5	182.6	121.9	10.1	22.4		24.1		
2,4,5-Trimethyl	196.0	132.5	172.8	47.5	189.8	122.2	16.0		14.7	24.2		
2,3,4-Trimethyl	192.1	130.9	188.0	48.5	174.4	122.3	16.0	?	?			
3,4,5-Trimethyl	194.4	121.4	198.4	50.9	188.3	121.4		24.3	13.7	24.3		

* In ppm from TMS.

† Assignment may be reversed.

Table 6. ^{13}C .M.R. Data for Ortho-Protonated Species in FSO_3H^* .

Parent Phenol	Ring Carbons						Methyl Positions			
	C_1	C_2	C_3	C_4	C_5	C_6	C_2	C_3	C_4	C_5
2,4-Dimethyl	205.9	?	174.1	?	?	42.5	14.0		19.7	
3,4-Dimethyl	201.8	120.4	193.7	137.8	148.2	40.3		25.4	17.6	
2,4,5-Trimethyl	201.3	128.8	180.0	134.5	164.6	47.0	13.5		17.1	20.7
2,3,4-Trimethyl	199.4	130.0	190.4	138.6	144.9	40.5	10.4	22.2	19.6	
3,4,5-Trimethyl	197.8	118.7	194.4	135.5	166.2	45.7		26.8	19.1	21.7

* In ppm from TMS.

(b) Ethyl-Substituted Phenols and Anisoles.

Table 7. Percentages of Protonation at each site^{†*}

Parent Compound	Oxygen	C ₄	C ₆
2,4-Dimethylphenol	65	6	29
2-Methyl-4-ethylphenol	48	23	29
3,4-Dimethylphenol	-	15	85
3-Ethyl-4-methylphenol	-	15	85
3-Methyl-4-ethylphenol	-	30	70
3,4-Diethylphenol	-	50	50
2,4,5-Trimethylphenol	-	83	17
2,4-Dimethyl-5-ethylphenol	-	90	10
2,5-Dimethyl-4-ethylphenol	-	96	4
2,4,5-Trimethylanisole	-	63	37
2,4-Dimethyl-5-ethylanisole	-	71	29
2,5-Dimethyl-4-ethylanisole	-	85	15

† Here and in the other tables in this section data for the analogous methyl-substituted compounds is included for ease of comparison.

* Solvent: FSO₃H

Table 8. P.M.R. Data for Para-Protonated Species in FSO_3H^*

Parent Compound	Ring Protons					Alkyl Substituents			Coupling
	C ₂	C ₃	C ₄	C ₅	C ₆	CH ₃	CH ₂ CH ₃	CH ₂ CH ₃	
2,4-Dimethylphenol	-	?	4.10q	?	?	2.33(C ₂), 1.58d(C ₄)	-	-	$J_{\text{Me,H}} = 7\text{Hz}$
2-Methyl-4-ethylphenol	-	?	4.05m	?	?	2.44(C ₂)	?	?	
3,4-Dimethylphenol	?	-	3.88q	8.26	?	2.66(C ₃), 1.62d(C ₄)	-	-	$J_{\text{Me,H}} = 7.5\text{Hz}$
3-Ethyl-4-methylphenol	?	-	3.90m	8.40	?	1.73d(C ₄)	?	?	$J_{\text{Me,H}} = 4.5\text{Hz}$
3-Methyl-4-ethylphenol	7.24	-	4.02m	8.50	?	2.65(C ₃)	2.35	0.77t	$J_{\text{Et}} = 7\text{Hz}, J_{45} = 2\text{Hz}, J_{56} = 10\text{Hz}$
3,4-Diethylphenol	7.45	-	4.12m	8.75	?	-	2.44m(C ₄), 2.83q(C ₃)	0.67t(C ₄) 1.38t(C ₃)	$J_{\text{Et}} = 7\text{Hz}, J_{45} = 2.5\text{Hz}, J_{56} = 11\text{Hz}$
2,4,5-Trimethylphenol	-	8.15	3.84q	-	7.15	2.29(C ₂), 1.65d(C ₄), 2.62(C ₅)	-	-	$J_{\text{Me,H}} = 7.5\text{Hz}$
2,4-Dimethyl-5-ethylphenol	-	8.33	3.88q	-	7.39	2.32(C ₂), 1.68d(C ₄)	2.94q	1.42t	$J_{\text{Et}} = 7\text{Hz}, J_{\text{Me,H}} = 7\text{Hz}$
2,5-Dimethyl-4-ethylphenol	-	8.28	3.95m	-	7.27	2.32(C ₂), 2.62(C ₅)	2.40m	0.73t	$J_{\text{Et}} = 7\text{Hz}$
2,4,5-Trimethylanisole	-	8.03	3.83q	-	7.43	2.25(C ₂), 1.62d(C ₄), 2.68(C ₅), 4.60(OMe)	-	-	$J_{\text{Me,H}} = 7.5\text{Hz}$
2,4-Dimethyl-5-ethylanisole	-	8.10	3.87q	-	7.49	2.33(C ₂), 1.70d(C ₄), 4.65(OMe)	3.07q	1.50t	$J_{\text{Et}} = 8\text{Hz}, J_{\text{Me,H}} = 8\text{Hz}$
2,5-Dimethyl-4-ethylanisole	-	8.17	3.92t	-	7.56	2.30(C ₂), 2.68(C ₅), 4.63(OMe)	2.35m	0.70t	$J_{\text{Et}} = 7\text{Hz}, J_{\text{CH}_2,\text{H}} = 8\text{Hz}$

*In ppm from TMS using $(\text{CH}_3)_4\text{N}^+$ as an internal standard.

d = doublet q = quartet m = multiplet

Table 9. P.M.R. Data for Ortho-Protonated Species in FSO₃H*

Parent Compound	Ring Protons					Alkyl Substituents			
	C ₂	C ₃	C ₄	C ₅	C ₆	CH ₃	CH ₂ CH ₃	CH ₂ CH ₃	Coupling
2,4-Dimethylphenol	-	8.34	-	7.10	4.25	2.33(C ₂ , C ₄)	-	-	
2-Methyl-4-ethylphenol	-	8.65	-	?	4.35	2.38(C ₂)	?	?	
3,4-Dimethylphenol	7.18	-	-	7.44	4.28	2.34(C ₄), 2.76(C ₃)	-	-	
3-Ethyl-4-methylphenol	7.17	-	-	7.39	4.28	2.35(C ₄)	3.09q	1.47t	J _{Et} = 7Hz
3-Methyl-4-ethylphenol	7.19	-	-	7.42	4.30	2.77(C ₃)	2.55q	1.33t	J _{Et} = 7Hz
3,4-Diethylphenol	7.42	-	-	7.60	4.37	-	2.55q(C ₄), 2.97q(C ₃)	1.38t(C ₃ , C ₄)	J _{Et} = 7Hz
2,4,5-Trimethylphenol	-	8.44	-	-	4.35	2.40(C ₂ , C ₄) ?(C ₅)	-	-	
2,4-Dimethyl-5-ethylphenol	-	8.61	-	-	4.33	2.32(C ₂ , C ₄)	2.94q	1.42t	J _{Et} = 7Hz
2,5-Dimethyl-4-ethylphenol	-	8.53	-	-	4.37	?(C ₂ , C ₅)	2.40m	1.23t	J _{Et} = 7Hz
2,4,5-Trimethylanisole	-	8.39	-	-	4.25	2.44(C ₂ , C ₄) ?(C ₅), 4.50(OMe)	-	-	
2,4-Dimethyl-5-ethylanisole	-	8.49	-	-	4.27	2.33(C ₂ , C ₄), 4.53(OMe)	2.88q	?	J _{Et} = 8Hz
2,5-Dimethyl-5-ethylanisole	-	8.52	-	-	4.25	2.30(C ₂), 2.45(C ₅), 4.50(OMe)	2.35m	1.20t	J _{Et} = 7Hz

* In ppm from TMS using (CH₃)₄N⁺ as an internal standard

d = doublet q = quartet m = multiplet

Table 10. P.M.R. Data for Oxonium Ions in FSO_3H^*

Parent Phenol	Ring Protons			Alkyl Substituents		
	C_3	C_5	C_6	CH_3	CH_2CH_3	CH_2CH_3
2,4-Dimethyl	7.30	7.30	7.30	2.40(C_2 , C_4)		-
2-Methyl-4-ethyl	7.45	7.45	7.45	2.33(C_2)	2.68q	1.27t

* In ppm from TMS using $(\text{CH}_3)_4\text{N}^+$ as an internal standard.

(c) Naphthols.

Table 11. Site of Protonation of Naphthols and Derivatives*

	Site of Attack
1-Naphthol	C_4
2-Naphthol	C_1
1-Methyl-2-naphthol	C_1
4-Methyl-1-naphthol	C_2 (50%) and C_4 (50%) [†]
4-Methyl-1-methoxynaphthalene	C_2 (77%) and C_4 (23%)
3,4-Dimethyl-1-naphthol	C_4
4,5-Dimethyl-1-naphthol	C_2 (10%) and C_4 (90%)

* Solvent: FSO_3H

[†] At -50°

Table 12. P.M.R. Data for Protonated Species in FSO_3H^*

Parent Compound	Site of attack	Ring					Protons			CH ₂	CHCH ₃	CH ₃	Coupling
		1	2	3	4	5	6	7	8				
1-Naphthol	C ₄	-	7.56d	8.74d	-	8.10	8.10	8.10	8.84	4.63	-	-	$J_{23}=10\text{Hz}$
2-Naphthol	C ₁	-	-	7.28d	9.17d	7.93 [†]	7.93	7.93	7.93	4.82	-	-	$J_{34}=9.5\text{Hz}$
1-Methyl-2-naphthol	C ₁	-	-	7.27d	9.15d	8.01 [†]	8.01	8.01	8.01	-	4.60q	1.97d	$J_{34}=9\text{Hz}$, $J_{\text{Me,H}}=8\text{Hz}$
4-Methyl-1-naphthol	C ₂	-	-	6.78	-	8.15 [†]	8.15	8.15	8.15	4.26	-	2.47	$J_{\text{CH}_2, \text{C}_3\text{H}}=2\text{Hz}$
4-Methyl-1-naphthol	C ₄	-	7.44d	8.73d	-	8.15 [†]	8.15	8.15	8.73	-	4.43q	1.78d	$J_{23}=10\text{Hz}$, $J_{\text{Me,H}}=8\text{Hz}$
4-Methyl-1-methoxynaphthalene	C ₂	-	-	6.84	-	8.16 [†]	8.16	8.16	8.16	4.18	-	2.49	
4-Methyl-1-methoxynaphthalene	C ₄	-	7.66d	8.65d	-	8.16 [†]	8.16	8.16	8.16	-	4.50q	1.77d	$J_{23}=10\text{Hz}$, $J_{\text{Me,H}}=8\text{Hz}$
3,4-Dimethyl-1-naphthol	C ₄	-	7.35	-	-	8.18 [†]	8.18	8.18	8.74	-	4.35q	2.75(C ₃), 1.75d(C ₄)	$J_{\text{Me,H}}=8\text{Hz}$
4,5-Dimethyl-1-naphthol	C ₂	-	-	?	-	-	?	?	?	4.25	-	2.75	
4,5-Dimethyl-1-naphthol	C ₄	-	7.37d	8.62d	-	-	7.83 [†]	7.83	8.49	-	4.65dq	2.75(C ₅), 1.62d(C ₄)	$J_{23}=9\text{Hz}$, $J_{34}=4\text{Hz}$, $J_{\text{Me,H}}=8\text{Hz}$

* Chemical shifts measured relative to $(\text{CH}_3)_4\text{N}^+$ as an internal standard

d = doublet q = quartet

† The centre of an unresolved overlapping multiplet

Table 13. Temperature Variation of the Isomer Ratio from
 Protonated 4-Methyl-1-naphthol

Temperature	<u>Para</u> -attack: <u>Ortho</u> -attack
-60°	0.97
-51°	1.06
-43.5°	1.20
-25°	1.47

DISCUSSION

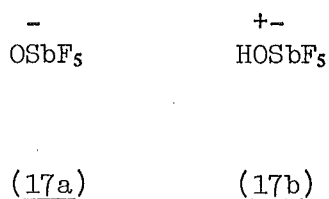
Phenols are ambident bases, that is to say they may be protonated either on a ring carbon or on the oxygen atom. Small changes in several variables may cause a significant change in the O:C-protonation ratio, and as a consequence the influence of each variable is not fully understood. However the site of attack appears to be determined by three interdependent factors : (a) the solvent system, (b) the substituents on the ring, and (c) the enthalpy and entropy of attack at each site.

As a result of the differing nature of the cations formed by protonation at either oxygen or carbon, the charge-stabilizing ability of the solvent is of major importance. Protonation on oxygen gives a cation with the positive charge located essentially on one atom, and consequently the stability of the ion depends largely on the hydrogen-bonding ability of the solvent as this is the most efficient method of spreading the charge. O-protonation, then, is favoured in such solvents as aqueous acids and HF, while an increase in the acidity of the medium favours C-protonation because the degree of proton transfer from the cation to the solvent will be less.

Solvation of the ring-protonated cation will be quite different as the charge is already considerably delocalized. The centres of positive charge will be on the ring carbons ortho and para to the site of attack as well as on the oxygen, and hydrogen-bonding will no longer be important. However the geometry of the solvent will become a significant factor, as its physical size will affect its ability to approach the centres of positive charge without

significant steric interaction with substituents. Clearly a solvent which can coordinate with more than one positive centre will have an advantage here.

There is another solvent effect which makes comparisons between different acid media difficult. In some solvent systems a Lewis acid such as BF_3 or, more usually, SbF_5 is added to increase the acidity. However it has been suggested⁷⁹ that this may result in a modification of the oxygen substituent, for example SbF_5 would give either (17a) or (17b) :



This not only affects hydrogen bonding but also reduces electron availability to the ring, and renders comparison of this system with a normal phenol molecule of debatable value.

In some acid systems, notably $\text{FSO}_3\text{H-SbF}_5$, the O:C-protonation ratio is found to be temperature dependent. O-protonation is favoured at low temperatures, i.e. the enthalpy of protonation on oxygen is less than on carbon. In FSO_3H temperature dependence effects are not usually observed, so if O- or C-protonation is favoured it implies that entropy differences are significant. If there is more oxygen than carbon protonation, then C-protonation requires more ordering of the solvent to stabilize the cation formed. With electron-releasing substituents on the ring, the necessity for solvation of the C-protonated ion is reduced, and as the oxonium ion is relatively

unaffected by ring substituents, entropy favours C-protonation. In general, the enthalpies of protonation of the two sites are very similar, and solvation differences govern the isomer ratios.

Phenol itself in FSO_3H is known to protonate entirely on the para ring carbon with no oxygen protonation being observed. This implies that the C-protonated cation requires less solvent stabilization than its O-protonated competitor.

While the foregoing outlines the effects which may determine the C-protonation : O-protonation ratio, it immediately raises another difficulty, namely the position of ring attack. Electrophilic attack on phenol seems to require that measurable amounts of protonation should take place ortho to the hydroxyl group. For example, the ortho:para ratio for nitration in organic solvents is approximately 60:40 in favour of ortho.⁸² Ortho attack was found to be favoured even more when nitration was carried out in nitric acid-acetic anhydride mixtures at low temperatures.⁸³ Halogenation shows a less marked tendency to high ortho:para ratios than nitration⁸⁴ (this could be a steric effect), but there is still substantial, sometimes predominant, ortho attack. These reactions are, of course, under kinetic control, and do not necessarily give a good indication of the likely product ratio in an equilibrium situation. However neither do they suggest a dramatic reversal to the extent that no ortho attack is observed.

The reason for this effect may lie in a modification of the phenolic-OH in acid solution. Solvation in the form of weak hydrogen-bonding from the acid to the phenolic oxygen would place a small

amount of positive charge on that atom, giving it a greater inductive withdrawing effect which would be felt most strongly at the ortho sites.

There is some evidence in the literature which provides support for this proposal. Yates and Stewart measured the basicities of substituted benzoic acids⁸⁵ and acetophenones⁸⁶ in sulphuric acid, and obtained a good correlation with the σ^+ values of the substituents. Deviations were found for p-OH particularly and for p-OCH₃, which were attributed to hydrogen-bonding from sulphuric acid to these substituents, reducing their ability to stabilize a positive charge.

A similar conclusion was reached when the NMR spectrum of anisole in acidic solvents was observed to differ from that in neutral solvents, with a downfield shift of all signals by up to 0.4ppm.³⁶ It was suggested that there is an interaction, e.g. hydrogen-bonding to the oxygen atom, which becomes stronger with increasing strength of the acid but does not alter the structure of the molecule in any fundamental way. An analogous gradual change in the UV spectrum of anisole in aqueous perchloric acid solutions has been observed and interpreted in a similar way.⁸⁷

Unfortunately there are no comparable examples in the literature of electrophilic attack on oxonium ions. The nearest is nitration of triphenyl oxonium ion⁸⁸ which indeed gives very little ortho attack, but steric compression at the ortho positions is substantial, and may be the major determinant of the product ratio.

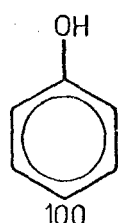
From this evidence it seems reasonable to postulate some

degree of positive charge on the oxygen from hydrogen-bonding. It will not be a full positive charge as the resulting substituent would be meta-directing and the chemical shifts are different from those reported for di-cations. On this basis one would predict that a methoxy group would give more ortho attack than hydroxyl as is observed; another consequence would be that in acid solution the effective size of the oxygen function will be rather larger than has previously been thought.

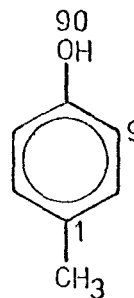
Alkyl substitution increases the activation of the ring so that carbon protonation predominates. The site of attack is determined by the directing effects of the substituents, and it is clear that the directing effect of the hydroxyl group is much more powerful than that of a methyl group. This is the reason for the exclusively para protonation of m-cresol, 2,3-dimethylphenol, 3,5-dimethylphenol, 2,6-dimethylphenol, and 2,3,5-trimethylphenol, despite the fact that in 3,5-dimethylphenol particularly, the arrangement of methyl groups is favourable for attack ortho to the hydroxyl group. This is in agreement with the published results of Childs⁷⁹ and Olah³⁹ whose work with 2,3-dimethylanisole and 3,5-dimethylanisole is consistent with this study of phenols. Although protonation of 2,6-dimethylanisole has been found to occur on oxygen in contrast to 2,6-dimethylphenol, this has been explained by reference to the steric requirements of the methoxy group.⁴⁰

However this pattern is upset by the introduction of a para-methyl substituent into the molecule. It was found in the methylbenzene series that the presence of a methyl group reduces the basicity

of the substituted site, and the same effect occurs in the phenols. While phenol (18) protonates entirely in the para position, p-cresol (19) protonates to the extent of 90% on oxygen and only 1% on the



(18)*



(19)

para ring carbon. In terms of energies, this represents a change of at least 12.5 kJ mol^{-1} in the relative stabilities of the para-protonated cation and the oxygen protonated cation (at -50°).

There are two possible explanations for this deactivating effect. The first is electronic in nature and was put forward by Brouwer, Mackor, and MacLean.²¹ They suggested that a methyl group will have a hyperconjugative interaction with the molecule, and any such mechanism for electron release would become even more important in the cation. Protonation at a methyl-substituted site means that the methyl group is bonded to an sp^3 hybridized carbon, and resonance interaction is impossible.

The alternative explanation involves steric inhibition of solvation. The ring-protonated cation will be stabilized partially by electron release from substituents and partially by solvation of the positive centres of the cation, two of which are adjacent to the

* In addition to the diagrams contained in the text, structures relevant to each section of the discussion are collected in fold-out diagrams at the end of the thesis. Figures refer to percentages of protonation at the site indicated.

site of protonation. If solvation takes place on both sides of the molecule, moving the methyl group out of the plane of the ring will hinder this solvent stabilization, and hence protonation at a substituted site is disfavoured.

As these two theories are complementary it is difficult to say which is likely to be correct; possibly both make a contribution as there is evidence for both effects in benzenonium ions. Koptug and coworkers²⁶ protonated a series of 1-alkyl-3,5-dimethylbenzenes and found a small preference for protonation para to a methyl group which they attributed to hyperconjugative interactions. However it has been found that in the gas phase, alkyl groups follow the inductive order in their ability to stabilize cations, as opposed to the Baker-Nathan order observed in solution. This does not favour the hyperconjugation theory, and Arnett⁸⁹ has recently commented that the reduction in solvation energy by increasing the bulk of the substituent probably has a steric origin.

For these reasons, then, the methyl substituent in p-cresol deactivates this site towards protonation, and the major site of attack is on oxygen, where solvent stabilization of the resulting cation is unhindered. This result is interesting in view of the confusion in the literature as to whether ring protonation takes place in FSO_3H . There is no doubt that in $\text{FSO}_3\text{H-SbF}_5$ solution substantial ring attack takes place ortho to the hydroxyl group,³⁹ but in the less acidic medium of pure FSO_3H , differing results have been obtained. Both Olah and Mo³⁹ and Bertholon and Perrin⁹⁰ observed solely oxygen protonation in this solvent, but Childs and Parrington⁷⁹ found 45% ring protonation, 40% at C_2 and 5% at C_4 . However they make the

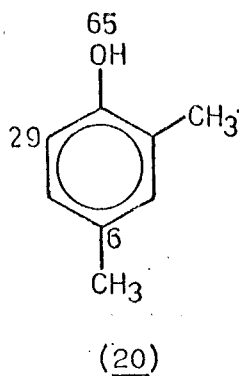
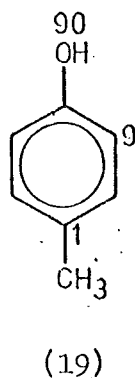
comment that the ratio of ring to oxygen protonation varies with different batches of acid, although the relative proportions of protonation at C₂ and C₄ do not. This behaviour was not observed with any of the other phenols, but nevertheless their results for the less activated phenols show more ring protonation than has been found by other workers. No reason was put forward for this phenomenon, but Larsen has reported that FSO₃H may contain small amounts of SO₃ because of the reaction of HF with glass during distillation. Coordination of SO₃ with the oxygen function will have a marked effect on the basicity of a phenol, and as a consequence comparisons between the protonation patterns of the weaker bases should not be made unless similar acid samples are used.

Further methyl substitution in p-cresol would be expected to increase the activation of the ring and thus reduce the proportion of oxygen protonation. If the effects discussed were the only considerations involved in determining the relative extent of protonation at each site, one might expect predictable changes in the protonation pattern with increasing methylation. However further complications undoubtedly arise from steric crowding between adjacent methyl groups; two such effects can be expected and one is well-documented for the methyl group.⁹¹ In a crowded environment, substitution at a methyl-bearing ring carbon should be favoured because the methyl is moved out of the plane of the ring and strain is consequently reduced. This steric compression has been demonstrated in desilylation reactions, where rates almost an order of magnitude above those predicted by additivity have been observed for protodesilylation and mercuridesilylation at SiMe₃ flanked by methyl groups.^{92,93}

Another steric factor is the well-documented buttressing effect which reduces the ring-activating effect of methyl groups in crowded environments. Reactivity is lower when the reaction site has ortho and meta methyl groups which are buttressed than when the methyl groups are unbuttressed (by about 17% in hydrogen-tritium exchange).

The complete set of product distributions from the nitration and acetoxylation of the polymethylbenzenes^{9,4} has been analysed in terms of four methyl partial rate factors - ortho, meta, para, and ipso. There is sufficient data from this protonation study to allow a similar calculation of a complete set of parameters (ρ , σ_{o-Me} , σ_{o-OH} , σ_{i-Me}) and σ_{p-OH} .^{9,5} However no consistent set of these parameters could be obtained from the data. It is possible to introduce an additional parameter to take some account of the effects of methyl buttressing^{9,1} but again a consistent set of values could not be obtained. This is not surprising as a different steric parameter would be necessary for each phenol, and in fact it is found that in the treatment of the nitration of methylbenzenes^{9,4}, to minimize the differences between predicted and observed results, the parameters must be varied in such a way that steric factors are clearly playing a significant role. As a consequence, therefore, the results of protonation of methylphenols may be discussed in qualitative terms only.

The addition of a second methyl group on the ring of p-cresol would be expected to decrease the necessity for solvation of a ring-protonated ion relative to the oxygen-protonated ion, and this is found to be the case. The amount of oxygen protonation drops from 90% in p-cresol (19) to 65% in 2,4-dimethylphenol (20), where the additional



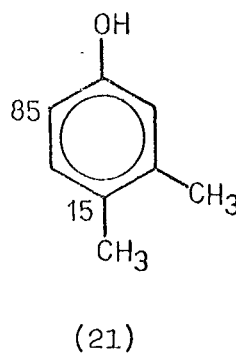
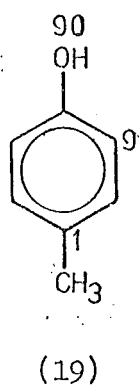
methyl group is not even in a particularly favourable position, as C_2 will be carrying little positive charge. The large change in the O:C-protonation ratio is a good illustration of the effect small energy differences may have on the protonation pattern. Predictably, the ratio of ortho attack to para attack is the same in 2,4-dimethylphenol as in p-cresol, once allowance is made for the statistical advantage of ortho attack in p-cresol.

The assignments for the cations from 2,4-dimethylphenol were carefully studied in view of the claims of Olah and Mo³⁹ that the corresponding anisole derivative is partially protonated on the meta position in FSO_3H . It is difficult to make a comparison between the chemical shifts published for the meta-protonated ion and those quoted here for the ortho-protonated ion as different reference compounds and acid systems are used, but their similarity suggests the two ions both result from ortho-protonation, as if proton addition had occurred at C_3 or C_5 , much different charge distributions and chemical shifts would be expected. Childs⁷⁹ has also investigated the possibility of meta-protonation in this system, and concluded that Olah's assignment is probably incorrect.

The most favourable circumstances for meta-protonation occur in 2,4,6-trimethylphenol, where methyl groups block the positions

ortho and para to the hydroxyl group, normally the most basic sites in the molecule. Furthermore, this same arrangement of methyl groups provides the greatest possible activation of the vacant meta positions which is possible in a methylphenol. However, even these factors are insufficient to overcome the directing influence of the hydroxyl group, and meta-protonation is not observed in FSO_3H . Childs⁷⁹ found protonation occurring on oxygen (42%) and on the para ring carbon (58%); the results of this study tend to confirm this, but the resonances of the ring protons were very broad, possibly due to the exchange rate being faster than normal in a compound of low basicity.

When the substituents on the ring are more favourably placed to stabilize ring-protonated cations, the amount of oxygen protonation falls away rapidly. 3,4-Dimethylphenol, (21), for example, is entirely ring-protonated, 85% at C_6 and 15% at C_4 . In p-cresol (19), the 2- and 6-positions are identical, but this would not be expected to be the



case in 3,4-dimethylphenol as the 3-methyl group should increase the basicity of the molecule rather more at C_6 than at C_2 . This expectation is realised with no protonation at C_2 being found, although Childs⁷⁹ reports the detection by NMR of about 3% attack at this site, an amount which is close to the experimental limit of the NMR technique.

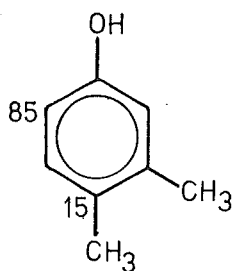
A major difference in protonation pattern between p-cresol and 3,4-dimethylphenol lies in the relative amounts of protonation at C₂ and C₄. In terms of electronic factors alone C₂ is favoured over C₄ by the same margin in both phenols, but while this is reflected in the 4.5:1 C₂:-C₄-protonation ratio in para-cresol, C₄-protonation predominates in 3,4-dimethylphenol. Clearly some other factor is operating here which is upsetting the predictions. The answer may lie in a steric clash between the two methyl groups which, for reasons previously discussed, would make protonation at the methyl-substituted C₄ more attractive.

There is evidence in the literature that this effect exists. For example, it has been shown by NMR⁹⁶ that in cis-but-2-ene there is indeed an appreciable overlapping of the van der Waals spheres of the methyl groups which does not occur in the trans isomer. A review of steric hindrance in aromatic hydrocarbons⁹⁷ compares the physical properties of ortho-dialkylbenzenes with those of meta- and para-dialkylbenzenes, and finds evidence of a "steric contraction" in the ortho isomers which results in repulsive forces which hinder rotation about the ring-methyl carbon-carbon bonds, leading to deformation of the angles between these bonds and a decrease in the internal energy of the molecule.

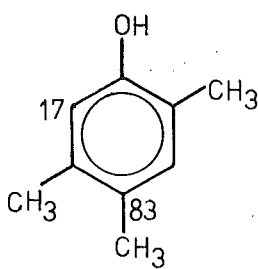
The size of this effect is not easy to determine with accuracy. As the C₂:-C₄-protonation ratio in both these compounds is based on a total of 15% or less of the cations present, and experimental error for any species is 2% at best, the uncertainty in the protonation ratio is necessarily large. Consequently it can be said only that the steric factor stabilizes protonation at C₄ in 3,4-dimethylphenol by between 1.5 and 5.5 kJ mol⁻¹. It is possible to get an estimate of the strain

energy in 3,4-dimethylphenol by comparing the heats of combustion of similar molecules. cis-But-2-ene is 3.1 kJ mol^{-1} less stable than the trans isomer,⁹⁸ and ortho-xylene is less stable than meta-xylene; with values^{99,100} ranging from 1.0 to 2.0 kJ mol^{-1} . However these values are small differences between large numbers, and have a large error associated with them, so they do no more than give an indication of the magnitude of the interaction. It appears to be of the same order as the steric effect observed, but it is impossible to say whether it is the complete answer or merely contributes to it.

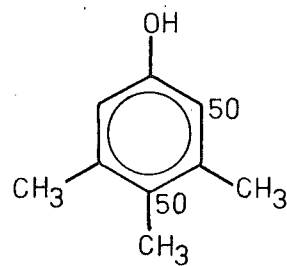
Protonating 2,4,5-trimethylphenol (22) is equivalent to protonating 3,4-dimethylphenol (21) with the most basic site (C_6) blocked by an ipso-methyl group. The ring carbons which are now competing for the proton are C_2 and C_4 (C_6 and C_4 in 2,4,5-trimethylphenol) which previously were insufficiently protonated to give an accurate indication of their relative basicities. The ratio of 83:17 in favour of para-



(21)



(22)



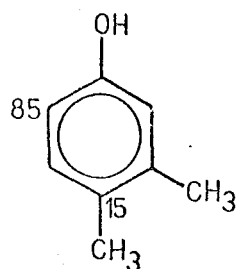
(23)

protonation over the vacant ortho position means that there should probably be about 3% protonation at C_2 in 3,4-dimethylphenol, an amount which may not be detected by NMR. 3,4,5-Trimethylphenol (23) is the first phenol where methyl buttressing is clearly of major importance. The most basic position in the molecule is found to be the para ring carbon, where 50% of the protonation takes place, with the

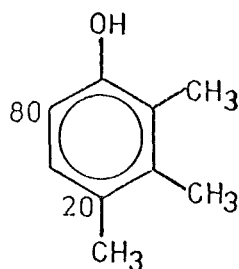
remaining 50% occurring equally on the two identical ortho sites. Again the comparison with 3,4-dimethylphenol is instructive, as electronically ortho-protonation should be even more predominant in 3,4,5-trimethylphenol than in the dimethyl compound. However the relief of steric strain is of such importance that the expected protonation pattern is drastically altered.

The strain introduced into a system by three adjacent methyl groups is well-documented. Calorimetric measurements of the heats of isomerization of propylbenzene into each trimethyl isomer give a value¹⁰¹ for the steric strain of 1,2,3-trimethylbenzene of $5.0 \pm 2 \text{ kJ mol}^{-1}$. This is in agreement with the work of Brown¹⁰², who found 4.2 kJ mol^{-1} difference in the activation energies of the reactions of pyridine and 2,6-lutidine with methyl iodide. The steric strain in 3,4,5-trimethylphenol will not be completely relieved by protonation of the 4-methyl group, but the relief of 4.2 kJ mol^{-1} of strain energy would change the protonation pattern from 83:17 in favour of C_6 over C_4 to 67:33 in favour of C_4 , and this is in good agreement with the observed change from 3,4-dimethylphenol to 3,4,5-trimethylphenol.

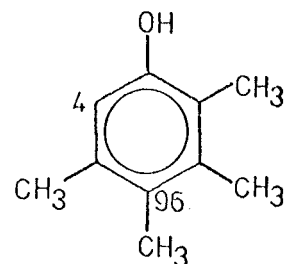
2,3,4-Trimethylphenol (24) should be at least as strained as 3,4,5-trimethylphenol, but protonation at C_4 will not relieve the strain to nearly the same extent. From electronic factors alone, the ratio of ortho-protonation: para-protonation should be the same as in 3,4-dimethylphenol (21), and in fact there is only a small change in favour of para attack, showing that the steric relief does not have a large effect.



(21)



(24)



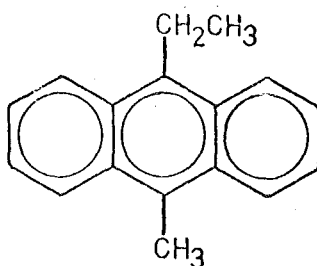
(25)

2,3,4,5-Tetramethylphenol (25) appears to be a very strained system and this is borne out by the results. The electronic effects are not as powerful as the need to relieve the crowding in the molecule, so it is not surprising to find 96% of the protonation on the para ring carbon.

The replacement of a methyl group in a phenol by an ethyl group, particularly on the site of protonation or in a position where it would be well placed to stabilize a positive charge, was found to have interesting consequences.

There are few examples in the literature of protonation of ethyl-substituted compounds, and even fewer of direct or indirect competition between ethyl- and methyl-stabilized cations. Olah¹⁰³ has studied a series of ethylbenzenium ions and found their properties to be similar to those of the analogous methylbenzenium ions, with the exception of the hexa- and hepta-substituted species which appear far more highly strained than their methyl counterparts. The influence of the size of the alkyl group was earlier noticed by Brouwer and

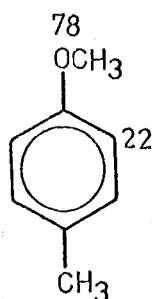
Van Doorn¹² when they protonated 9-ethyl-10-methylanthracene (26).



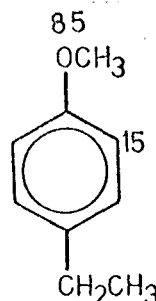
(26)

The alkyl groups are in electronically equivalent positions, but far more attack took place at C₉ than C₁₀ because of the greater relief of steric interaction with the α -hydrogens obtained by protonating ipso to the ethyl group.

When internal steric strain is not a factor, there appears to be a delicate balance of smaller effects which determines whether ethyl is activating or deactivating with respect to methyl. During the course of a study of the ambident behaviour of phenols, Larsen⁴¹ reported the results of protonating p-methylanisole (27) and



(27)

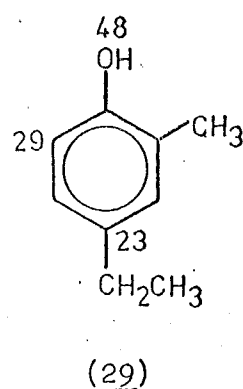
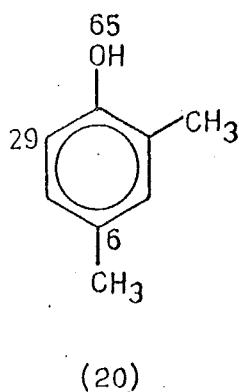


(28)

p-ethylanisole (28) in FSO₃H. He found an O:C-protonation ratio of

3.5:1 for the former compound and 5.5:1 for the latter (C-protonation is at C₂), i.e. the ethyl group is having a smaller activating effect on the ring than methyl. As no explanation was advanced for this behaviour, we prepared other ethyl-substituted phenols and the results of protonation compared with those of the methylphenols previously discussed. 2-Methyl-4-ethylphenol was selected as a system where O-protonation is a competitor, and its protonation pattern contrasted with that of 2,4-dimethylphenol. A study was also made of more activated substrates, using 3,4-dialkylphenols and 2,4,5-trialkylphenols and trialkylanisoles with combinations of methyl and ethyl groups in the meta and para positions.

In contrast to Larsen's results, in all these compounds ethyl was found to be more activating than methyl, both in terms of protonation ipso to the para substituent and in terms of the O:C-protonation ratio. 2-Methyl-4-ethylphenol (29) protonates 48% on oxygen, 29% on C₆ and 23% on C₄ compared with 65%, 29%, and 6% for the same sites of 2,4-dimethylphenol (20). The drop in oxygen



protonation in the former case may simply be a result of the greater inductive effect of ethyl than methyl, which is felt more strongly on the ring than on oxygen. That this effect is significant is seen in

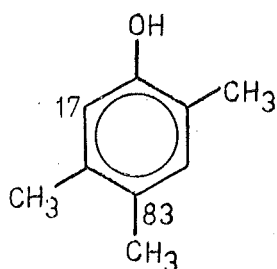
the greater stability of ethylbenzenium ions over toluenium ions in the gas phase,²⁷ which removes the large effect of the solvent. Solvation differences, though, are responsible for the lowering in stability of the C₆-protonated cation relative to the C₄-protonated cation when the ethyl group is introduced. It was earlier postulated that protonation ipso to an alkyl group is not favoured because moving the alkyl group out of the plane of the ring interferes with solvation on that side of the cation. The ethyl group however is large enough to hinder this solvation to some degree even without protonation at that site, and this problem may outweigh its greater inductive effect and render it less able to stabilize a cation than a methyl group. Protonation will be more favoured ipso to an ethyl group than a methyl group for this reason, as less solvent stabilization is lost by moving the ethyl group out of the plane of the ring.

The relative effect, then, of ethyl versus methyl depends on a balance of two effects: the greater inductive effect of ethyl, and its hindrance of solvation. Larsen's results with p-methylanisole and p-ethylanisole⁴¹ may be explained on this basis, as the ring-protonated cations of these compounds will require more solvent stabilization than those of the dialkylphenols, which have an extra electron-releasing group on the ring. The resistance to solvation imposed by the ethyl group is consequently more important, and outweighs its greater inductive effect so that p-methylanisole shows more ring protonation than its ethyl analog. However, as in the case of the methylphenols, the energy differences involved in the above discussion are very small (no more than 1.3 kJ mol⁻¹). In view of the small amount of data available, the explanation proposed above must be treated with caution

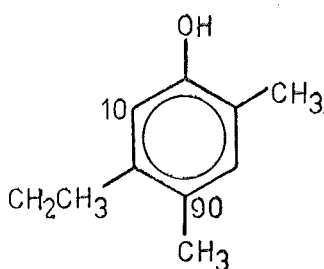
until increasing knowledge allows us to rationalize small energies, particularly solvent-solute interactions, with more confidence.

The result of ethyl substitution is rather easier to rationalize in a series of more activated phenols where the position is not complicated by oxygen protonation. In the 2,4,5-trialkylphenols and anisoles and the 3,4-dialkylphenols competition for the added proton is restricted to two ring sites, and the effect of introducing an ethyl group can be judged from the way it alters the position of equilibrium between the two cations.

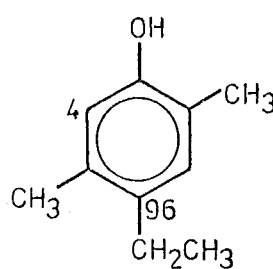
The most simple effects are seen in the trialkylphenols. The protonation of 2,4,5-trimethylphenol (22) has already been discussed; 17% occurs ortho to the hydroxyl group on C₆, and 83% para to the hydroxy group, ipso to the C₄ methyl. The result of replacing the C₅ methyl group with an ethyl group (30) is very slight, the ratio altering from 83:17 to 90:10. This represents a change in the free energy difference between the two isomers of about 1.0 kJ mol^{-1} (at -50°),



(22)



(30)



(31)

favouring the para-protonated cation. Electronically, the change of substituent should affect both sites equally, as it is ortho to both C₄ and C₆. Similarly, if the view of solvation taken by this study is correct, the relative solvating abilities of the two cations should not be altered. The likely reason for any change towards attack at C₄ is a small increase in the steric strain between the adjacent alkyl groups at C₄ and C₅. Accurate values for methyl-methyl and methyl-ethyl interactions are not available, but heats of combustion¹⁰¹ suggest that the methyl-ethyl system is indeed slightly more strained.

A similar steric effect is expected when the C₄ methyl group of 2,4,5-trimethylphenol is replaced by an ethyl group. However there is also a second effect to be considered: less solvation is lost protonating ipso to an ethyl group than ipso to a methyl group. This also pushes the molecule towards more para attack than in 2,4,5-trimethylphenol, so the observation of 96% para attack in (31) is not surprising.

The effects observed in the 2,4,5-trialkylphenols are closely paralleled in the 2,4,5-trialkylanisoles [(32), (33), and (34)]. The only difference is that the amount of protonation observed at C₆ is always greater than that observed in the corresponding phenols. The changes in protonation pattern, however, with the substitution of ethyl for methyl, are of the same magnitude and in the same direction.

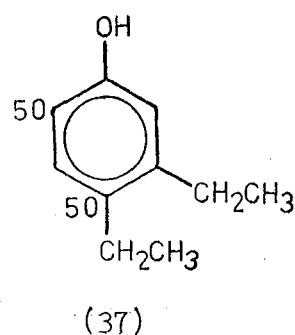
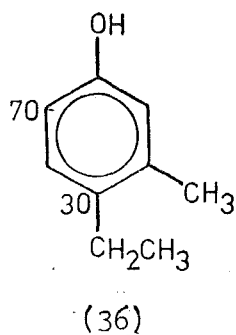
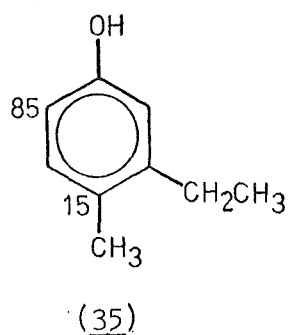
The 3,4-dialkylphenols also give a mixture of two ring-protonated ions, the most basic sites in the molecule being C₆ and C₄.

3,4-Dimethylphenol protonates in these positions in the ratio of 85:15,

no protonation at C₂ being detected although the isomer ratio from the protonation of 2,4,5-trimethylphenol suggests that trace quantities may occur.

Substitution of ethyl for methyl in this system should exhibit the same effects that were seen in the 2,4,5-trialkylphenols, with one important addition. The protonated site C₆ now has a para alkyl substituent at C₃, and it is known¹⁰⁴ that an alkyl group has its greatest effect on basicity when it is in this orientation with respect to the position of attack. Hence any difference in the electronic activating powers of ethyl and methyl will be most noticable here, as no other protonated site in the 3,4-dialkylphenols or 2,4,5-trialkylphenols is similarly activated.

This factor is clearly seen in a comparison between 3,4-dimethylphenol (21) and 3-ethyl-4-methylphenol (35). Both these phenols protonate 85% at C₆ and 15% at C₄, despite the greater steric strain between the alkyl groups in the latter case, which should facilitate attack at C₄. However this "steric activation is counter-balanced at C₆ by the greater electronic activation of an ethyl group than a methyl group and the relative basicities of C₄ and C₆ remain unchanged.



3-Methyl-4-ethylphenol (36) retains the steric activation at C₄ but not the electronic activation at C₆, so it is not surprising to find 30% attack at C₄ compared with 15% in 3,4-dimethylphenol. The decreased resistance to protonation ipso to an ethyl group compared with protonation ipso to a methyl group also favours attack at this site.

In 3,4-diethylphenol (37) steric factors are beginning to dominate with 50% protonation at C₄, where the steric clash between the adjacent ethyl groups can be partially relieved. There are other factors which must also be considered: the greater ease of protonation ipso to an ethyl group rather than a methyl group, and the greater electronic activation of a para ethyl group compared with a para methyl group. Estimates of the energies involved in these factors of about 1.5 kJ mol⁻¹ and 0.85 kJ mol⁻¹ respectively can be made from the results of protonation studies on the other dialkylphenols and trialkylphenols. The transition from 15% C₄ protonation in 3,4-dimethylphenol to 50% in 3,4-diethylphenol requires a change in the free energy difference between the two cations of about 3.1 kJ mol⁻¹, and combining that with the values above implies that the diethylphenol is about 2.5 kJ mol⁻¹ more restrained than the dimethylphenol. Again no accurate figures for steric strain are available, but heats of combustion of diethylbenzenes¹⁰⁵ indicate that this would be about the middle of the range.

It is clear that the substitution of one alkyl group for another will not have a simple effect on the protonation reaction. A combination of several factors, all involving small energies, will decide the overall result. The differences in the electron-releasing

powers of the alkyl groups appears to be the least important factor; steric effects within the molecule and with solvating species are the major causes of change.

Protonation of phenols with substituents other than alkyl did not lead to any useful results, as it was difficult to devise a system where ring attack could take place without side-reactions.

The strong electron-withdrawing power of the halogen proved to be the dominant influence on the protonation of 2-bromo-4,5-dimethylphenol. Here, in contrast to the 100% ring attack on 2,4,5-trimethylphenol, protonation in FSO_3H at -50° occurred almost entirely on the oxygen. However at -28° trace amounts of attack on C_4 and C_6 were detectable, but this was insufficient to determine the effect of the bromine on their relative proportions.

2-Nitro-4,5-dimethylphenol was also found to be insufficiently activated to sustain ring attack. In view of the previous result this is not surprising as the nitro-group not only has an electron-withdrawing effect on the ring, but also provides alternative basic sites within the molecule. Raising the temperature did not appear to assist ring-protonation, and at -18° decomposition began. An attempt was made to identify the products of the decomposition, but GLC traces of quenched reaction mixtures showed that the breakdown was not consistent. decomposition was not entirely unexpected as nitroalkanes have been shown to cleave in $\text{SbF}_5\text{-FSO}_3\text{H}$ solution leading to formation of carbonium, nitronium, and hydronium ions.¹⁰⁶ However the reaction is obviously sensitive to substituents as ortho-, meta-, and para-nitrophenol are all stable in FSO_3H at room temperature.

The substitution of a second oxygen function on the aromatic ring was more successful in stimulating a protonation reaction, but the results were again inconclusive. 1,2-Dimethoxy-4,5-dimethylbenzene in FSO_3H solution gave a very broad, poorly resolved NMR spectrum at low temperatures but a sharper spectrum emerged as the temperature was raised. At -10° , three pairs of singlets were obtained, centred at $\delta 2.5$, 4.5 , and 7.5 , and integrating as 6, 6, and 2 protons respectively (methyl, methoxy, and ring protons). The spacing within each pair was 0.7ppm for the methyl and methoxy peaks and 0.5ppm for the ring protons. On the surface this spectrum appears to be consistent with protonation on one oxygen, removing the symmetry of the molecule, but there are objections to this interpretation. Firstly, it is easy to see why one ring hydrogen should be deshielded considerably more than the other, but not why the effect should be greater for the methyl groups. Secondly, one methoxy group should be split by the added proton unless the exchange rate is quite high. However a rapid exchange rate would involve both oxygens and could not give rise to an unsymmetrical cation.

Two further compounds were synthesised with substituents one carbon removed from the aromatic ring rather than directly bound to it, in the hope that their protonation patterns would be similar to that of the parent trimethylphenol. Unfortunately the NMR spectra of 2,5-dimethyl-4-hydroxymethylanisole and 2,5-dimethyl-4-chloromethylanisole in FSO_3H were broad and insufficiently resolved at all temperatures to allow any identification of cations.

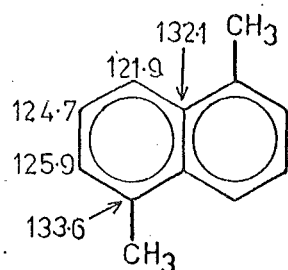
Protonated naphthalene derivatives have not been studied to any great degree, as protonation work in general has concentrated more on benzene series, where substrates are easier to obtain. The most recent work¹⁰⁷ was prompted by a desire to fill a gap in the literature in that both benzenium and anthracenium ions had been observed but naphthalenium ions had not. Anthracenium ions are formed very much more easily than benzenium ions as considerable resonance stabilization is retained in the cation, and it was expected that naphthalenium ions would also form more readily for this reason. However it would appear that the difference in stabilities is not very great as in $\text{SbF}_5\text{-HF-SO}_2\text{ClF}$ solution benzenium ions are stable below -130° , naphthalenium ions at -80° .¹⁰⁷

Other naphthalene compounds examined in this paper follow the same protonation pattern as their benzene analogs. Halonaphthalenes protonate ortho and para to the substituent, ortho protonation involving initial attack on the halogen followed by migration to the ring. Methylnaphthalenes give one isomeric ion only, and as in the methylbenzenes, less stable cations may isomerize via 1,2-hydrogen and 1,2-methyl shifts.

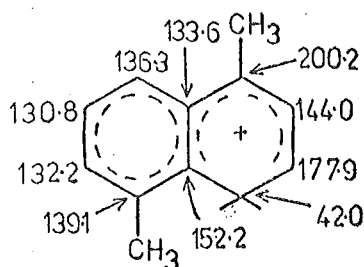
It appears from this data that the presence of the second aromatic ring in naphthalene derivatives has little effect on the protonation reaction in the substituted ring. Given that diprotonation does not occur, there are two possible ways in which this new factor might influence the reaction: (a) the stability of the cation could be enhanced by delocalization of the positive charge into the second ring, and (b) the proximity of substituents on C_4 and C_5 (or C_1 and C_8)

may introduce new steric factors into the system which, as well as making the relief of strain important, could affect solvent stabilization of the cation. This study makes it clear that both these effects play a part in determining the pattern of protonation in naphthols.

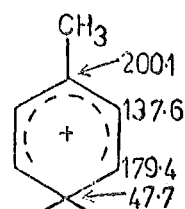
Delocalization of positive charge into the second ring would not be expected to be very extensive as this would involve considerable loss of resonance energy. As carbon magnetic resonance reflects electronic structure and charge distribution rather better than proton magnetic resonance, a comparison was made between the ^{13}C chemical shifts of 1,5-dimethylnaphthalene (38) and its cation (39) in $\text{HF-SbF}_5\text{-SO}_2\text{ClF}$. It was found¹⁰⁷ that while a dramatic change occurred in the chemical shifts of the protonated ring, very little change took place in the



(38)



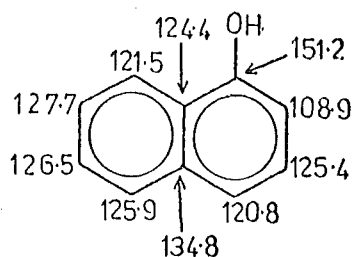
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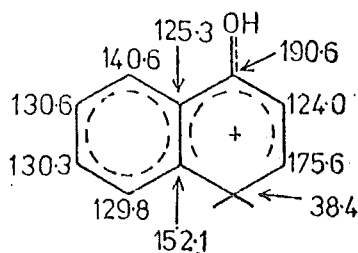
(40)

second ring, indicating that it retained most of its aromatic character.

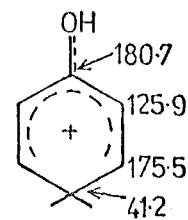
To check that this non-involvement of the unprotonated ring was not a function of the substrate or the solvent, the CMR spectrum of 1-naphthol (41) was compared with the spectrum of its cation (42) in FSO_3H . As in the work previously described, the chemical shifts of



(41)



(42)



(43)

the carbon atoms in the protonated ring are very similar to those of the analogous benzenoid cation (43), while the unprotonated ring appears to be basically unchanged.

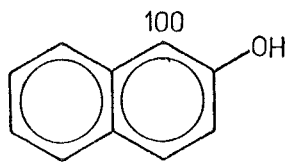
This conclusion, however, is only valid if there is a good correlation between ^{13}C chemical shifts and charge densities. While this is true for neutral molecules, it may not be so for charged systems. Recent work¹⁰⁸ with substituted benzoyl cations showed only poor correlation, in contrast to earlier studies of di- and triphenylmethyl cations where good agreement was obtained. The problem may well lie with the CNDO/2 calculated charge densities, but at present conclusions based solely on ^{13}C chemical shifts must be regarded with caution.

For electrophilic attack on naphthalene, it is possible to draw more canonical forms of the σ -complex which retain the aromaticity of the second ring for attack at the 1-position than for attack at the 2-position. Thus the 1-position is generally the preferred site of attack although the product of substitution at the 2-position is thermodynamically more stable. However with a substituent such as hydroxyl on the ring, this preference should become less marked as the

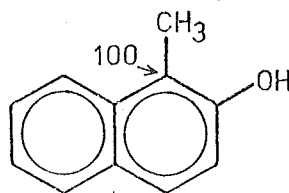
canonical forms of the σ -complex will be dominated by that with the positive charge residing on the oxygen, and the other forms will assume a lesser importance.

1-Naphthol, as illustrated above, protonates only on C₄. Like phenol, it appears to be resistant to ortho attack both because of the postulated solvent coordination to the hydroxyl substituent and the greater stability of the σ -complex formed by attack in this position. The NMR spectrum has many similarities to that of protonated phenol, particularly with regard to the chemical shifts and coupling constants of hydrogen atoms on the protonated ring. However there is an added point of interest in that the C₈ proton is deshielded by about 0.7ppm more than the rest of the unprotonated ring. This large peri effect is taken to mean¹⁰⁷ that the carbon-oxygen linkage has strong double bond character, which is consistent with the picture of electron donation by the oxygen.

There is a choice of sites ortho to the oxygen function on which 2-naphthol (44) could be protonated. In the event, C₁ proved much more basic than C₃, as no protonation was observed in the latter position. This structure assignment was made entirely from the PMR spectrum, which shows a high field doublet at $\delta 7.28$ (C₃H) and a slightly broadened low field doublet at $\delta 9.16$, consistent with the C₄ hydrogen having weak long-range coupling to the methylene.



(44)

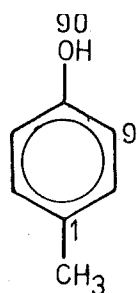


(45)

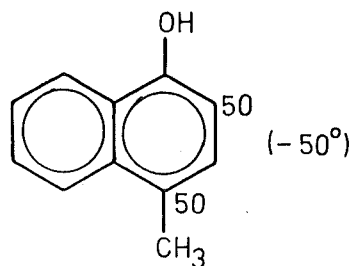
The large difference in basicity between C_1 and C_3 in 2-naphthol is further demonstrated by the protonation of 1-methyl-2-naphthol (45). It is known from the methylphenol series that protonation ipso to a methyl group is not favoured because of interference with the solvation of the cation, but despite this, 1-methyl-2-naphthol protonates entirely at C_1 , with no trace of attack at C_3 being detected.

There are two reasons for this selectivity. The first is seen in the preference of naphthalene itself to protonate at C_1 rather than C_2 because of the greater stability of the σ -complex from attack at the former site. Substituents may alter the size of this effect, but the causes of it are still applicable to 1-methyl-2-naphthol. The second reason lies in the steric strain between the methyl group and the peri proton at C_8 . The difference in the heats of combustion of 1-methylnaphthalene and 2-methylnaphthalene¹⁰⁹ shows a strain energy of about 12.5 kJ mol^{-1} , so any release of this strain resulting from attack at the methyl-substituted site increases the stability of this cation.

The same factors should operate in 4-methyl-1-naphthol (46), which can profitably be compared with p-cresol (19). In the latter compound, ortho attack is preferred to para attack by a ratio of 4.5:1, but the presence of the second ring in 4-methyl-1-naphthol changes this ratio to 1:1 at -50° . Protonation ipso to the methyl group is favoured



(19)



(46)

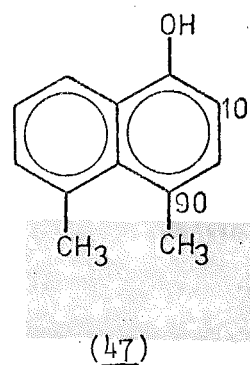
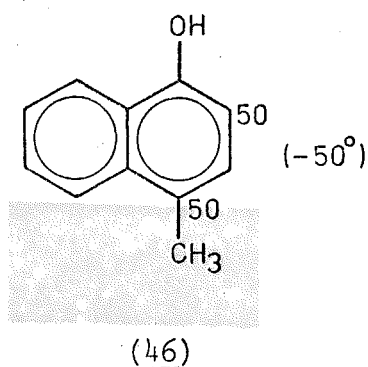
by the steric clash with the peri proton at C₅, while protonation ortho to the oxygen function is disfavoured by the lower stability of the σ -complex formed by attack in this position. However the most interesting comparison between 4-methyl-1-naphthol and p-cresol considers the amount of oxygen protonation in each case: 90% in p-cresol and none in 4-methyl-1-naphthol. Assuming the relative stabilities of the two oxygen-protonated cations to be similar, it appears that the carbon-protonated cations from 4-methyl-1-naphthol are at least 8.4 kJ mol^{-1} more stable than their counterparts from p-cresol. Steric relief may cause the difference between the para-protonated ions, but in the ortho-protonated ions it should be a measure of the delocalization of positive charge into the unprotonated ring of the naphthol - obviously there must be a balance between the stabilization gained by spreading the positive charge over as much of the molecule as possible, and the resonance energy lost by involving the second ring.

It is clear that the steric strain in 4-methyl-1-naphthol will be considerably less than that which must arise in 3,4-dimethyl-1-naphthol and 4,5-dimethyl-1-naphthol, and that relief of strain will therefore dominate the course of protonation in both these two compounds. However

as no figures are available for the strain energies, it is necessary to try to assess the relative degree of strain in each.

One such estimate has been made* using a method based directly on the "strained homomorph" concept of Brown.¹⁰² Values of steric strain in methylnaphthalenes were obtained by studying the Menschutkin reaction of quinoline derivatives of similar geometry, and 1, 2-dimethylnaphthalene is thus accorded a steric strain of 14 kJ mol⁻¹, 1, 8-dimethylnaphthalene 31 kJ mol⁻¹ (c.f. 35 kJ mol⁻¹ from recent X-ray¹¹⁰ and thermodynamic¹¹¹ studies). The magnitudes of these figures may be unreliable as other strain energies estimated by this method are widely distributed around more recent values obtained by direct calorimetric methods. However it is sufficient to observe that 1, 8-dimethylnaphthalene should be more strained than both 1-methylnaphthalene and 1, 2-dimethylnaphthalene.

4,5-Dimethyl-1-naphthol (47) shows the effect of being more strained than 4-methyl-1-naphthol (46) by protonating 90% at C₄ and only 10% at C₂. A comparison of the PMR spectra of the cations from



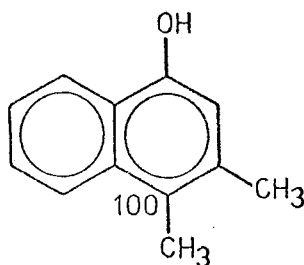
these two naphthols gives clear evidence of the greater steric relief obtained by protonating ipso to the 4-methyl group in 4,5-dimethyl-1-naphthol. The C₄ hydrogen in this cation is coupled to the C₃ hydrogen, and

* J. Packer; J. Vaughan; E. Wong, J. Amer. Chem. Soc. (1958), 80, 905.

As 3, 4-dimethyl-1-naphthol (48) is less strained than 4, 5-dimethylnaphthol, one might have expected correspondingly less ipso protonation. The observation of 100% protonation at C₄ of the former compound therefore calls for some explanation.

There are two methods of stabilizing a cation, (a) solvation of the positive charge, and (b) charge spreading by electron-donating substituents. Method (a) predominates for less basic substrates but becomes less important with increasing substitution. 3, 4-Dimethyl-1-naphthol should therefore be less dependent on solvent stabilization of its cations than is 4, 5-dimethyl-1-naphthol, as it has an extra methyl group on the protonated ring, and the loss of solvation associated with ipso attack should be less important. Thus solvent effects appear to be more important than steric effects in determining the relative amounts of protonation at C₄ in these two naphthols.

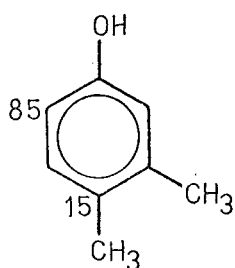
the size of the coupling constant is a function of the angle between the two C-H bonds. The coupling constant $J = 2.5\text{Hz}$ for the cation from 4-methyl-1-naphthol, and 4Hz for the similar cation from 4,5-dimethyl-1-naphthol may be interpreted to mean that in the latter case the C_4 proton is closer to the plane of the ring system and the geminal methyl group correspondingly further from the plane, thus getting greater relief from the sterically interacting group on C_5 .



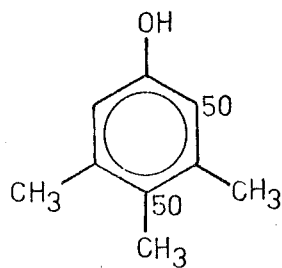
(48):

It is an interesting fact that the strain energies which direct the paths of protonation in naphthols are much larger than those which are found in the methylphenol series, but despite this their effect appears to be smaller. The strain energies in the phenols studied here are all less than 8.5 kJ mol^{-1} , but this is sufficient to bring about 96% para attack (where strain is best relieved) in the most hindered case. However in the naphthols, even the 35 kJ mol^{-1} strain in 4,5-dimethyl-1-naphthol does not exert complete control over the site of protonation and 10% ortho attack is found.

These observations prompted a closer look at the amount of steric relief obtained by protonating ipso to a buttressed methyl group. Particularly striking is the comparison of 4-methyl-1-naphthol with 4,5-dimethyl-1-naphthol, which should have very similar electronic activations at the most basic sites but which differ by 23 kJ mol^{-1} in strain energy. However the respective ortho:para protonation ratios of 50:50 and 10:90 suggest that only 4 kJ mol^{-1} of this extra strain is relieved by protonating at C_4 . The same calculation on 3,4-dimethylphenol (21) and 3,4,5-trimethylphenol (23) where the additional methyl group should have an equal electronic effect on both sites of attack (C_4 and C_6), finds that the extra 4 kJ mol^{-1} of strain



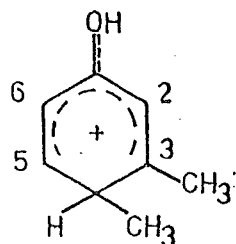
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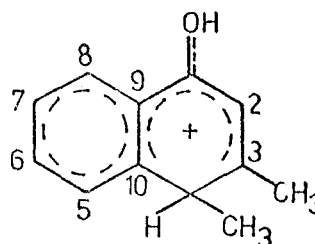
(23)

energy is balanced by an increase in stability of the para-protonated cation over the ortho-protonated cation of about the same amount, i.e. the extra strain imposed on the system by the third methyl group is very largely relieved by attack at C_4 . Thus it would appear the release of strain associated with protonation ipso to a buttressed methyl group is greater in the methylphenols than the methylnaphthols.

Steric relief is obtained through the rehybridization of the



(49)



(50)

protonated carbon (C_4 in the phenol (49) and naphthol (50) above), which by going from sp^2 to sp^3 swings the C_4 -methyl group out of the plane of the aromatic ring and away from the other substituents. If the environment around C_4 is very crowded, extra relief may be obtained by a distortion of the bond angles at C_4 which moves the methyl group out of the plane and the geminal proton correspondingly closer to the plane. Evidence for this effect in naphthalenes has already been discussed, and it is also believed to occur in the methylphenols. However the rehybridization has a second effect: it slightly distorts the planarity of the ring towards the boat conformation, and this distortion increases the further the C_4 -methyl group moves out of the plane. Thus in phenols, C_1 and C_4 both move upwards and a little towards each other, but in the naphthols the constraint applied by the unprotonated ring results in C_1 and C_4 being held in the molecular plane, but C_2 and C_3 rising up above it. The mean plane of the protonated ring therefore becomes tilted with respect to that of the unprotonated ring, and any conjugation involving both rings will be reduced. The results of protonating 4-methyl-1-naphthol show that the cations obtain at least 8.4 kJ mol^{-1} of stabilization energy from delocalization of positive charge into the unprotonated ring, so any distortion of the molecule caused by the relief of steric strain may cause some of this stabilization energy to be lost.

Protonation of a naphthol at C₂ will not give rise to the same problems as only one sp² carbon (C₃) can be moved out of plane, and that not to the same extent as C₂ and C₃ in the para-protonated cation. There will also be no tendency to distort the bond angles of the protonated carbon to move a substituent further out of the plane, as protonation is occurring at an unsubstituted site.

This discussion was prompted by the observation that the strain energies in naphthols do not direct the course of protonation to the extent expected by analogy with the methylphenols. It appears that while the molecular distortions which result from protonating a methylphenol in the ortho or para position are similar, the same cannot be said for the ortho and para sites of a methylnaphthol; para-protonation may result in loss of conjugation with the unprotonated ring and consequently a greater gain of steric relief is required to encourage protonation at this site than is the case in methylphenols.

Some confirmation of earlier proposals regarding the solvation of cations was obtained unexpectedly when the isomer ratio from the protonation of 4-methyl-1-naphthol was found to be temperature dependent. The variation seen was small but reversible, with protonation occurring equally ortho and para to the hydroxyl group at -60°, but para-attack being favoured 59:41 at -25°.

An analogous transformation has also been observed by a group of Russian workers.¹¹² They found that in 4-bromo-1-naphthol, 4-methyl-1-naphthol, and 1-naphthol itself, the ortho-protonated cations were wholly or partially converted to para-protonated cations as the temperature was raised, with the conversion being irreversible for

the halogenated compound.

There are few such cases reported in the literature of temperature dependence of isomer ratios from protonation reactions. Temperature dependence is usually of a different type, for example the temperature dependent PMR spectrum obtained from the rapidly equilibrating 1- and 2-protonated naphthalenium ions,¹⁰⁷ or the freezing out of rotational isomers at low temperatures.

One example of two ring-protonated cations in equilibrium is reported by Brouwer and Van Doorn¹²: the protonation of 9-ethyl-10-methylantracene in HF takes place at the 9- or 10-position, with the latter being favoured by 7.5:1 at -20° and 4.0:1 at $+70^{\circ}$. However this type of equilibrium is more commonly seen in the temperature dependent isomer ratios of the C-protonated and O-protonated ions derived from phenols and phenol ethers. O-protonation is favoured at low temperatures but decreases in importance as the temperature is raised. Larsen⁴¹ has made a considerable study of this topic using an $\text{SbF}_5\text{-FSO}_3\text{H}$ solvent; temperature dependence is a manifestation of the difference in the enthalpies of protonation on oxygen and on carbon, and a rough estimate of this difference may be obtained from a Van't Hoff plot of $1/T$ against the log of the isomer ratio. The results are quantitatively uncertain, as the NMR technique is too imprecise to yield reliable enthalpies, but they give an idea of the magnitude of the energies involved.

These calculations show that the two basic sites have similar heats of protonation : for p-methylphenol in 10% $\text{SbF}_5\text{-FSO}_3\text{H}$ the

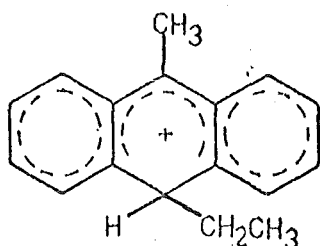
enthalpy difference is 5850 J mol^{-1} , and for *p*-methylanisole the difference is 2900 J mol^{-1} in 20% SbF_5 - FSO_3H and $18,800 \text{ J mol}^{-1}$ in 33% SbF_5 - FSO_3H^* . Thus, particularly with a low SbF_5 concentration, small changes in conditions can cause large shifts in the ratio of O-:C-protonation.

Similar calculations can be made with the isomer ratios from 4-methyl-1-naphthol. The difference between the enthalpies of protonation of the two sites is about 5450 J mol^{-1} , while the difference in the entropies of protonation is $25 \text{ J deg}^{-1} \cdot \text{mol}^{-1}$. Ortho-protonation is therefore more exothermic, but para-protonation requires less ordering of the solvent. This is consistent with the theory that protonation ipso to a methyl group interferes with solvation on one side of the cation.

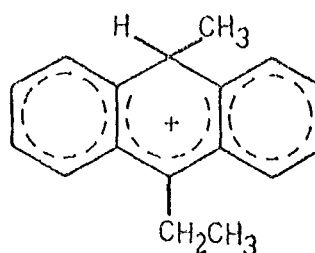
Attempts to investigate the temperature dependence further by varying the oxygen function met with no success. 1-Methoxy-4-methyl-naphthalene (51) was 77% protonated at C_2 and 23% at C_4 with no variation with temperature, while 1-acetoxy-4-methylnaphthalene rapidly cleaved in FSO_3H to give 4-methyl-1-naphthol.

While the data provided by Brouwer and Van Doorn¹² does not allow any worthwhile calculations to be made, it appears that the differences in enthalpy and entropy of protonation at the two protonated sites in 9-ethyl-10-methylanthracene are similar to those found in 4-methyl-1-naphthol. This also helps to outline the picture of

* These are not the figures quoted in Larsen's paper. His calculations appear to be in error, but the conclusions drawn would not be much affected by the correction.



(7a)



(7b)

$$(\underline{7a})/(\underline{7b}) = 7.5 \text{ at } -20^\circ, \quad (\underline{7a})/(\underline{7b}) = 4.0 \text{ at } +70^\circ$$

solvation of cations, as the entropy effects show that ion (7b) is solvated to a lesser extent than ion (7a), i.e. protonation at the ethyl group causes less hindrance to solvation than protonation at the methyl group, as was postulated when discussing the ethyl-substituted phenols.

The object of this project was to study molecules with substituents on the basic sites to gain information on the factors governing the position of protonation and the mechanisms of stabilizing cations. At the beginning of this discussion it was suggested that the position of protonation in phenols is determined by three interdependent factors: (a) the solvent system, (b) the substituents on the ring, and (c) the enthalpy and entropy of attack at each site, with (c) being a function of (a) and (b).

When this work was begun, the observed effects of the substituents were mainly restricted to their electronic directional influences. Steric strain within a molecule had been known to affect the site of attack,^{28,40} but was not a common factor as most compounds protonated were insufficiently activated either sterically or electronically to sustain ipso-attack, this being the situation where steric effects are most obvious. This study shows that when there is close competition

for the proton between two or more basic sites, steric relief is often important in determining the site of attack or the isomer ratio. However as steric hindrance has been observed to affect the course of nitration of polymethylbenzenes,⁹⁴ a similar result for protonation was not unexpected.

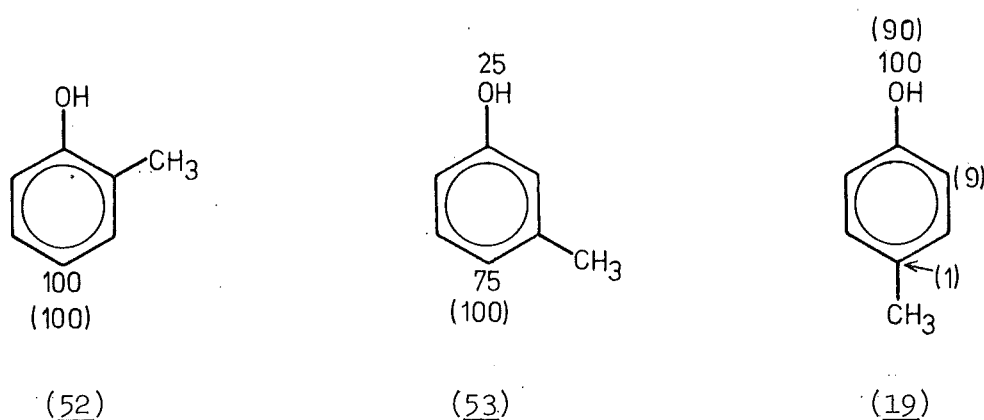
The effect of the solvent on the protonation reaction now appears to be considerably greater than was originally thought. The debate as to whether anisole protonated on oxygen or carbon soon raised the point that good hydrogen-bonding solvents favour oxygen attack while more powerful acids protonate the ring. Solvent stabilization of oxonium ions, then, was well known, but the case for solvation as a significant method of stabilizing benzenium ions was not nearly so strong as any evidence for it could equally well be explained by hyperconjugation. However the recent publication of results which show that alkyl groups follow the inductive order in their ability to stabilize protonated benzene in the gas phase, and the reverse order in superacid solution²⁷ makes it clear that solvation of charge on the aromatic ring is very important. Such effects as the reduced tendency to protonate a substituted site and the differing activating powers of a substituent in two different molecules can therefore be explained by interactions with the solvating species, and the relative stabilities of two ring-protonated isomers may well depend on the solvent. A carbon-protonated phenol, for example, will have three centres of positive charge on the ring as well as a positively charged oxygen as a result of electron donation; charge distribution will vary for isomeric cations and isomer ratios will be determined by the success of the solvent in coordinating with all positive centres.

Further research in this area would thus be most profitably directed towards a systematic study of solute-solvent interactions. Anything which helps to draw a picture of solvated cations must help immeasurably the understanding of their relative stabilities. Some of the important factors immediately spring to mind: the polarizability of the solvent, a geometry which minimizes clashes with substituents (not so applicable to oxonium ions), and an ability to coordinate with more than one charge centre.

However such a study may encounter practical difficulties as several of the popular superacid media would be unsuitable. One problem is alteration of the substrate by the solvent; for example it has been suggested⁷⁹ that SbF_5 , which is a common component of highly acid mixtures, may co-ordinate with the oxygen of a phenol and convert it into an electron-withdrawing group. Similar uncertainty as to the final form of the substrate exists with the cations formed from complexing phenols and naphthols with aluminium halides.

The exact composition of the solvent, which must be known for any study of solvation, is another doubtful factor in several acid media. $\text{FSO}_3\text{H}-\text{SbF}_5$ solution contains a complex mixture of species which varies with SbF_5 concentration, and problems have also occurred using only FSO_3H . Childs⁷⁹ has found different O-C-protonation ratios for p-cresol in different batches of the acid, and suggested that it may be caused by dissolved SO_3 . Even the effect of such supposedly inert diluents as SO_2 and SO_2ClF may not be straightforward as Larsen⁴¹ reports that the addition of SO_2 to a mixture of cations lead to the development of NMR signals other than those of oxonium or benzenium ions.

If the practical problems could be overcome, however, much information could be gained from the protonation of selected molecules in different solvents. A very interesting example of this has already been published, but the full significance of the results was not appreciated at the time. Olah³⁹ protonated the three isomeric cresols in $\text{FSO}_3\text{H-SO}_2\text{ClF}$ solution (relative concentrations were not given) and found the percentages of protonation at the basic sites as shown in



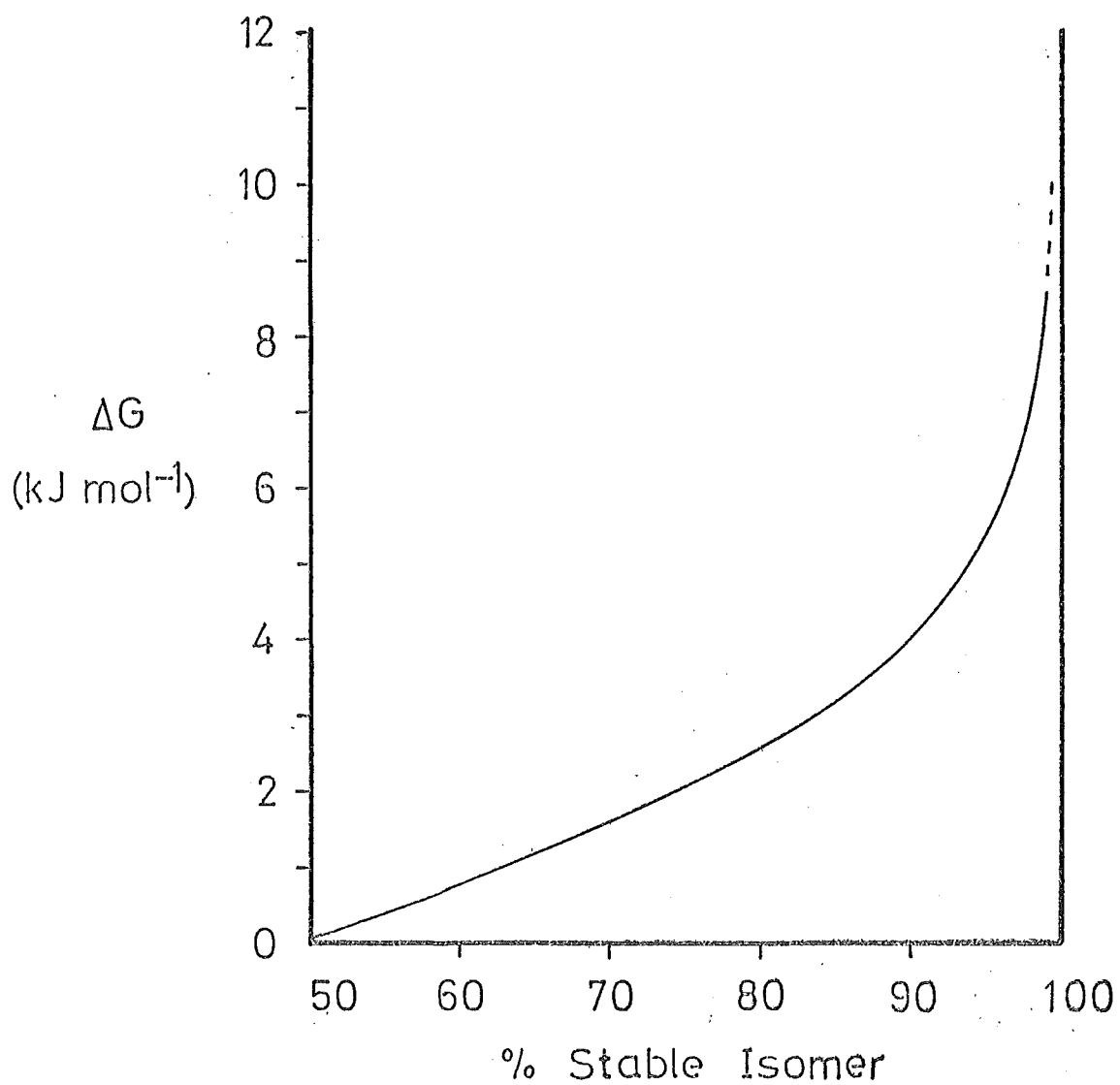
the diagrams. The results of protonation in pure FSO_3H are shown in brackets. The different solvating abilities of the two solvents are very evident. FSO_3H appears to be better at solvating the ring than $\text{FSO}_3\text{H-SO}_2\text{ClF}$, and the comparison between *o*-cresol and *m*-cresol in the latter solvent shows steric hindrance which does not occur in FSO_3H . Either the ortho-methyl group is hindering solvation of the oxonium ion or the meta-methyl group, which is bonded to a centre of positive charge, is affecting solvation of the ring.

Reliable data of this kind may be difficult to obtain, but is essential for the understanding of the protonation reaction. Until solvent effects in superacid media are the subject of careful study,

our knowledge of cation stabilities must remain incomplete.

APPENDIX

The relationship between free energy difference and isomer ratio at -50° .



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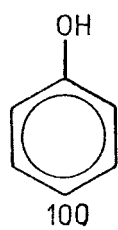
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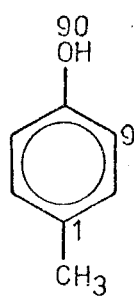
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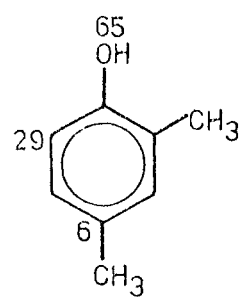
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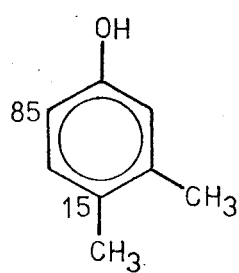
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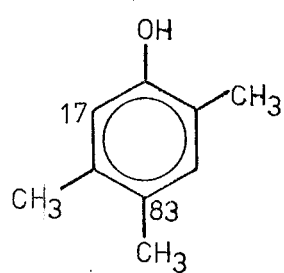
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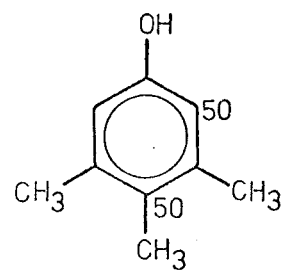
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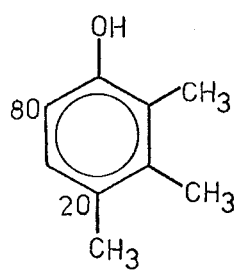
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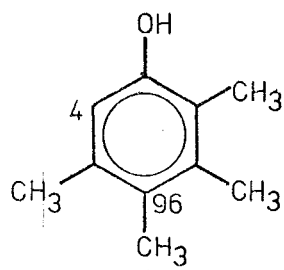
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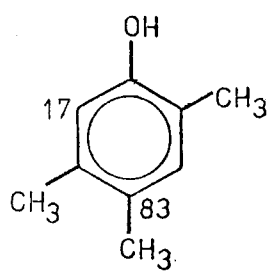
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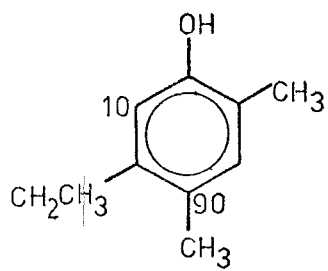
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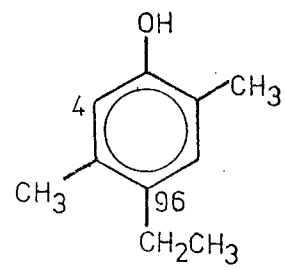
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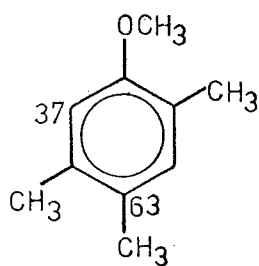
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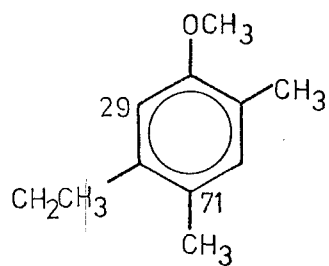
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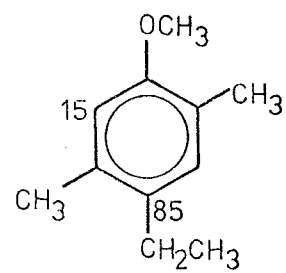
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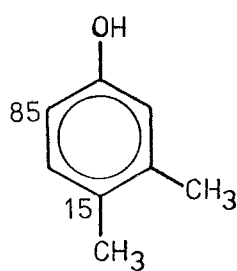
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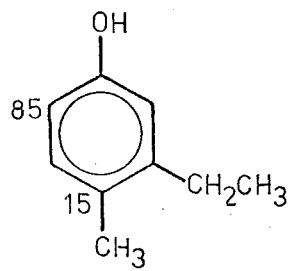
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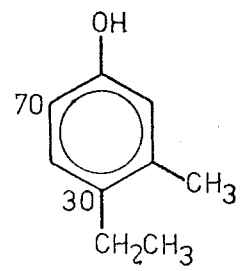
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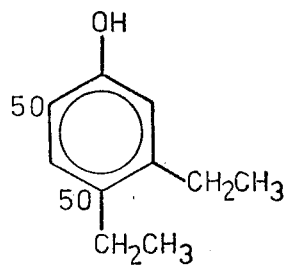
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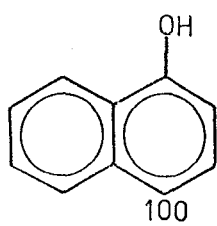
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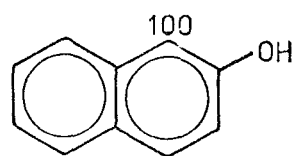
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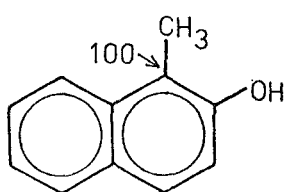
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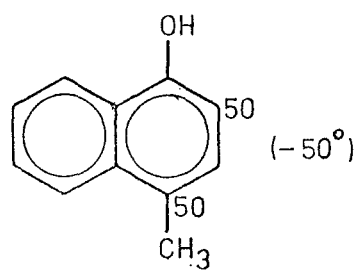
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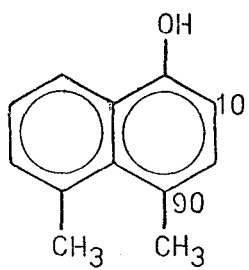
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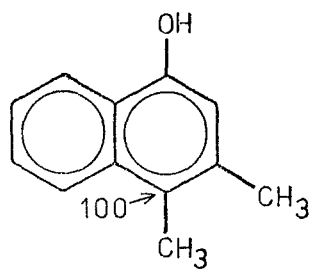
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